Disorders of the Circulatory System

Edited by

ROBERT L. CRAIG, M.D.

A SYMPOSIUM

Presented at the Twenty-fourth Graduate Fortnight of The New York Academy of Medicine, October Eighth to Nineteenth, 1951

Disorders of the Circulatory System

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FOREWORD

THE Graduate Fortnight has been a featured annual event in the educational program of The New York Academy of Medicine for the past twenty-four years

The Fortnight was first proposed in February 1927 by the late Dr. Ludwig Kast, a member of the Committee on Medical Education of the Academy He suggested that a two-week period be devoted annually to a general review of progress in a subject of special current interest.

In recent years this symposium has included a series of twenty Evening Lectures, four Morning Panel Discussions, twenty Afternoon Hospital Clinics, and a Scientific Exhibit.

This volume, the second of the published series, presents the collected papers of the evening programs of the Twenty-fourth Graduate Fortnight of The New York Academy of Medicine which was held October 8 to 19, 1951, on the subject, "Disorders of the Circulatory System"

Grateful acknowledgment is due The Macmillan Company for its cooperation and helpful advice and to Miss Diane Joffe of the Academy staff for editorial assistance in the preparation of this volume

The Editor

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ADDRESS OF WELCOME
The Twenty-fourth Graduate Fortnight *

WILLIAM BARCLAY PARSONS
President, The New York Academy of Medicine

IT IS a privilege and pleasure to welcome all of you on behalf of The New York Academy of Medicine to the first session of its twenty-fourth Graduate Fortnight, which now is officially opened.

Twice before, in 1931 and in 1941, certain aspects of disease of the circulatory system formed the basic subject matter for discussion. The Committee in charge of arranging the program for this Fortnight decided that there have been sufficient advances during the past ten years to make it almost mandatory to take the Disorders of the Circulatory System as the subject matter for discussion

The Academy welcomes the collaboration of the New York Heart Association in this Graduate Fortnight As you can see from the program its President, Dr. Irving S Wright, and Vice President, Dr. Charles A. Poindexter, have been active members of the main Committee and have contributed greatly in the preparation of the program All the members of the Committee have done a magnificent job, and we owe them a heart-felt vote of thanks In particular we should mention Dr. William Dock, who as Chairman of the whole Committee, worked out the program and saw to it that the various sub-committees completed their assignments, Dr Alfred Angrist, who has planned and executed the Exhibit, and Dr Clarence de la Chapelle, who has arranged the Panel Discussions. To Dr Mahlon Ashford, who has resigned after many years of service as Executive Secretary of the Committee on Medical Education, we owe an especial debt of gratitude His has been the guiding hand that over

* Presented October 8, 1951, at the 24th Graduate Fortnight of The New York Academy of Medicine

PREFACE

THE New York Academy of Medicine devotes its best efforts to presenting clinics and authoritative lectures on an important aspect of medicine for one fortnight each autumn. The cardiovascular system is re-examined on this occasion about every ten years. In 1951 the liveliest topics were those dealing with biochemical aspects of pathogenesis and surgical methods of treatment.

The committee in charge of this program can only express its deep gratitude to all those who participated in this presentation, and to the Fellows of the Academy and to the members of The New York Heart Association whose advice and help were so generously given.

Many of the contributions require the careful study and digestion which can only come from reading, even though the personal presentation was stimulating and enlightening. For those who were present, and for many others, this book has been prepared. We believe it is a sound and detailed discussion of this field of medicine, which will be valuable to all who practice medicine.

WILLIAM DOCK, M.D.
Professor of Medicine, State University of New York, College of Medicine, Chairman, Graduate Fortnight Committee, The New York Academy of Medicine

the years has made these Graduate Fortnights such outstanding successes. Although behind the scenes, quiet and unobtrusive, his organizing genius has simplified the duties of the volunteer committees, and I feel sure that each one of them agrees with me. Our thanks are due to our friends here in town who will deliver papers, hold demonstrations, or have prepared exhibits. Lastly I thank on behalf of the Academy our visitors from out of town: Drs. Blumgart, Gofman, Szent-Gyorgyi, Dexter, Stead, Katz, Page, Duryee, Kossmann, and Hunter, who have come from North, West, and South to make their contributions for our interest and education in those subjects in which they are admittedly masters.

The program for the evening meetings covers metabolism, chemistry, physiology, surgery, radiology, psychiatry, and therapeutics The clinical meetings in various hospitals will cover a wide field of subjects, and the exhibits here in the Academy do not fall short of the excellence of previous years. We are sure that the menu which is in your hands indicates that a highly nutritious mental repast has been prepared for your enjoyment. I therefore wish you "Bon appetit."

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Chapter 1

THE ROLE OF THE CONNECTIVE TISSUE IN DISEASES OF THE CARDIOVASCULAR SYSTEM *

Paul Klemperer †

CONNECTIVE TISSUE fundamentally participates in the construction of the cardiovascular system. It is obvious that in a discussion of morbid states of this system serious consideration must be given to the role played by the connective tissue. For instance the valvular deformities characteristic of chronic rheumatic heart disease, or the intimal changes of arteriosclerosis, are the result of an abnormal overproduction of connective tissue substance. Textbooks refer to inflammation as the cause of the former, to metabolic disturbances as effective in the latter. But such general pathologic explanations give no account of the intrinsic biologic and chemical mechanisms which operate to produce an increase of connective tissue substance. An understanding of the cardiovascular alterations must rest upon a comprehension of the basic factors which are responsible for the imbalance of growth of the connective tissue, which means that interest in diseases of the cardiovascular system necessitates a consideration of the connective tissue problem.

What is the problem? Divested of all the secondary questions of cellulation, which have attracted the attention of biologists for more than a century, it is the relationship between the cells and the intercellular substances The problem did not exist before the discovery of the connective tissue cell by Schwann (1), because previous investigators (Haller) had considered the fiber as the only elementary constituent. The recognition of two or more components, cells, fibers, and a homogeneous intermediate substance, necessarily led to the question of their genetic re-

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† From the Department of Pathology, Mount Sinai Hospital, New York, N Y.
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lationship. While Schwann (1) and Henle (2) believed that cells and intercellular substances develop from a formless, mucoid cytoblastema, the ancestral form of the living substance, Reichert and Virchow (3) proposed the primacy of cells. Schwann (1) assumed that fibers develop in the connective tissue directly from the cells, while Henle (2) believed that the residual original cytoblastema also gave rise to fiber formation. Reichert and Virchow (3) maintained that the cells alone can form fibers, though not by a transformation of the cytoplasm but through the formation of a secretion which subsequently undergoes fibrillation. Accordingly Virchow (3) postulated that the intercellular substances were not endowed with vital activity. Schwann's (1) and especially Henle's (2) original theory is today of historical interest only because the idea of a primordial formless cytoblastema became untenable with the discovery of cellular division as the universal form of organic development, clinched by the famous pronouncement of Virchow (4) *omnis cellula e cellula* However, the belief in an independence of the intercellular substances from formation by local cells, to which Henle (2) subscribed though based on an erroneous conception, retained its validity and has been supported by subsequent investigations. In fact, the origin and source of the intermediate substances of the connective tissue seems to me to be one of the most crucial problems of modern pathology.

Contemporary investigations of the connective tissue were dominated by Virchow's doctrine of the primary importance of the cells, and the intermediate substances were stripped of biologic significance. Only the cells were capable of irritation, of metabolism, and of reproduction. According to Virchow, they were endowed not only with a great power of proliferation but also capable of almost universal transformation. They formed a sort of germinal layer which gave rise to all the cells of the inflammatory territory and to many neoplasms. While this exaggerated importance of the cells of the connective tissue was successfully challenged by Cohnheim (5) and his school and by Thiersch (6), Waldeyer (7), and others, the intercellular substances continued to exist in their neglected role as a material formed for the one purpose only, to fill in and to support the nobler elements of the human body. Only Stricker and Grawitz tried to give biologic dignity to the intercellular substances by proposing that they could revert to connective tissue cells This hypothesis takes its origin from Schultze's and Flemming's (8) beliefs

that the connective tissue fiber is not the product of a secretion of the connective tissue cell (the later fibroblast) but of a transformation of part of its cytoplasm, which Hansen (9) subsequently called the ectoplasm. This theory gained more and more momentum through the publications of Studnicka (10) and Wassermann (11). It was introduced by Hueck (12) into the interpretation of pathologic states affecting the connective tissue, specifically for the explanation of arteriosclerosis. According to this theory, the cytoplasm of the cells of the mesenchyme *primarily form* an interconnected syncytium. The perinuclear cytoplasm, referred to as endoplasm, is the metabolically most active part from which in its further development an outer layer, the ectoplasm, becomes demarcated. This metabolically less active outer layer of the undivided *cytoplasmic* syncytium is transformed into the extracellular ground substance of the mesenchyme and develops fibers. The fibrillar differentiation is to be *considered* as a vital, structure-forming process because the ectoplasm is still endowed with some, though reduced, vitality. Cells and fibers remain genetically united and represent the living matter in its totality. This concept of the relation between cells and extracellular substances is based upon *investigations* of human embryonal and adult connective tissue supplemented by studies of lower forms of animals.

The alternative theory regards the intercellular substances as a secretory product of the connective tissue cells. As mentioned before, this concept originated with Virchow, was fully accepted by Koelliker and subsequent investigators, and is still recognized by the *majority* of histologists (Stearns) (13). *Virchow* (3) was aware of the ectoplasm theory, first promulgated by Schultze. It is of more than historical interest to refer to his statements in refutation. He believed that the discussion whether fibers *originate* from cellular secretion or from a metamorphosed cytoplasm was *only* an academic argument. "Because the concept of a secretion *of* the intercellular substance *takes* it also for granted, that the secretory *product* originally was contained within the cell . . ." and ". . . nobody has yet demonstrated that the cortical layer of the connective tissue corpuscles is actually transformed into intercellular substance." One can add *that conversely no irrefutable* proof has yet been supplied either for a *secretion* of the intercellular substances by the connective tissue cells. This state of *our* information makes it necessary not to neglect the original idea of Schwann (1) and Henle (2), who thought

lationship. While Schwann (1) and Henle (2) believed that cells and intercellular substances develop from a formless, mucoid cytoblastema, the ancestral form of the living substance, Reichert and Virchow (3) proposed the primacy of cells. Schwann (1) assumed that fibers develop in the connective tissue directly from the cells, while Henle (2) believed that the residual original cytoblastema also gave rise to fiber formation Reichert and Virchow (3) maintained that the cells alone can form fibers, though not by a transformation of the cytoplasm but through the formation of a secretion which subsequently undergoes fibrillation. Accordingly Virchow (3) postulated that the intercellular substances were not endowed with vital activity. Schwann's (1) and especially Henle's (2) original theory is today of historical interest only because the idea of a primordial formless cytoblastema became untenable with the discovery of cellular division as the universal form of organic development, clinched by the famous pronouncement of Virchow (4): *omnis cellula e cellula*. However, the belief in an independence of the intercellular substances from formation by local cells, to which Henle (2) subscribed though based on an erroneous conception, retained its validity and has been supported by subsequent investigations. In fact, the origin and source of the intermediate substances of the connective tissue seems to me to be one of the most crucial problems of modern pathology

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by cells of mesenchymal derivation. Nageotte (20) in his classical book categorically denied the origin of the collagen fibers from fibroblasts. According to his opinion they are formed by precipitation from the albuminoids of the milieu internal of Claude Bernard, i. e., from the universal body fluids That fibers can develop from a colloidal medium under the influence of mechanical forces had already been shown by von Ebner. It remained for Nageotte (21) to demonstrate that collagen fibers can be precipitated from a cell- and fiber-free acid solution of collagen by neutralization or addition of salt. His observations were confirmed and further expanded by Huzella (22) and his associates, who showed that fiber formation from a homogeneous solution of collagen is under the exclusive control of physicochemical forces. In ingenious in vitro experiments he succeeded in producing fiber frameworks whose architecture simulated that of various organs and tissues of the living organism. These artificial fiber systems could be populated by bringing them in contact with living heterogeneous cells in tissue cultures. F O Schmitt and his associates (23) could show that the fibers precipitated from an acid solution of rat tail collagen have the characteristic periodicity of collagen fibers under the electron microscope In recent experiments (Highberger, Gross, and Schmitt) (24) it was demonstrated that through interaction of pro-collagen and plasma mucoprotein collagen fibers are produced. Therefore there is evidence that collagen fibers can develop without the intervention of specific cells Nageotte (20) and Huzella (22) deny the existence of a genetic relationship between intermediate substances and connective tissue cells and maintain that the material necessary for their formation is derived from the tissue fluids which in turn receive their contributions from the metabolism of the entire body While this contention has not been proven it is well to remember that the formation of the intercellular substances by the fibroblasts has never been unequivocally demonstrated either. In the present uncertainty it seems advisable to refrain from the premature interpretation that quantitative or qualitative abnormality of the intermediary substances of the connective tissue invariably denotes abnormality of the fibroblast.

It is for the same reason that I prefer the term "collagen disease" (Klemperer, Pollack, and Baehr) (25) with all its admitted inadequacy, to the apparently conciser term connective tissue or mesenchymal disease with its cellular pathologic connotation The term "collagen disease"

of deposition of intermediate substances independent of connective tissue cells. Baitsell (14) was the first to use the dynamic method of tissue culture for the investigation of fiber formation and came to the startling conclusion that collagen fibers can be formed without the interaction of fibroblasts. Because he postulated a transformation of fibrin into collagen fibers and because the newly formed fibers were not resistant to trypsin digestion, Baitsell's far-reaching conclusions were generally not accepted. However, the belief in an extracellular formation of collagen fibers found forceful support by the investigations of Maximow (15) and his school and a great number of subsequent students of tissue cultures. Their conclusions were finally clinched by the studies of Porter and Vanamee (16), who showed that the fibers formed in cultures of fibroblasts of different vertebrate species showed characteristic periodicity under the electron microscope and that they resisted trypsin digestion.

Yet even these brilliant results of in vitro experiments have not solved the fundamental connective tissue problem. The relationship between fibroblasts and intermediate substances of the connective tissue in vivo is still obscure because we do not yet know enough about the interaction between cell and medium in vitro. Porter (17) in recent, not yet published, studies found that fibroblasts cultured in protein-free Locke's solution can form fibers, but that fiber formation is accelerated and augmented upon addition of plasma. The question is raised again as to the relative importance of the living cell and the lifeless ground substance of the tissue culture. This is the first problem which underlies the riddle of the diseases characterized by abnormalities of the connective tissue. In vitro experiments seem to leave no doubt that fibroblast and collagen fiber formation are intimately bound together. Accepted school doctrine postulates the same for the living organism. Yet there are facts, not so widely known, which contradict the conventional belief of an exclusive genetic relationship *between the mesenchymal cell and collagen fiber.* Von Ebner (18) as long ago as 1896 demonstrated that collagen fibers develop in the notochord sheath of lower fish without the presence of mesenchymal cells. Reed and Rudall (19) demonstrated the presence of fibers with the characteristic *x-ray diffraction pattern of collagen within the* ectoderm of the earthworm, although they did not show the periodicity under the electron microscope. These disclosures indicate that the material necessary for collagen fiber formation is not supplied exclusively

were digested by trypsin. This proved first that they were of proteinic nature but not identical with collagen. In later years Dr. Feitelberg of our Physics Laboratory by wide angle x-ray diffraction examined endocardial vegetations in this disease which, we believed, originate from intravalvular fibrinoid deposits. It was shown that they did not contain collagen, the x-ray diffraction pattern was that of a mixture of proteins but not characteristic. Recent investigations, carried out by Drs. Gueft and Laufer (32) at Mount Sinai, and the Fairfield State Hospital, have thrown light upon the origin and nature of the fibrinoid substance deposited within the wall of glomerular capillaries and of arteries. These studies took their origin from our old observations (33) of hyaline thrombi within the glomerular capillary lumen and our recent analysis of the hematoxylin bodies (34) It was noted that some of the homogeneous eosinophilic plugs showed smudged particles stained with hematoxylin. These particles were Feulgen positive and could therefore be identified as desoxyribose nucleic acid It was thus suggested that they were the remnants of a progressive depolymerization of the DNA and that the major part of the hyaline thrombi consisted of the protein moiety of the nucleoprotein. In order to test these deductions appropriate histochemical determinations were carried out. The hyaline thrombi and wire loops are digested by trypsin, they are Millon positive, strongly absorbing the light of a mercury vapor lamp of 3650 A wave length This proves the presence of tyrosin containing protein The non-histone protein is such a compound. According to White (35) histone stains strongly with orange G if submerged in a mixture of aniline blue and orange G at pH 3 The hyaline thrombi and wire loops stain selectively yellow under such circumstances. The results of the histochemical studies therefore support the assumption that the hyaline thrombi are the products of a progressive degradation of nucleoprotein of which the hematoxylin bodies represent an earlier phase. Since the wire loops stain identically with the hyaline thrombi within the capillary lumen the conclusion seems justified that they consist of the same material which has impregnated the basement membrane The fibrinoid of larger vessels is tinctorially identical with that of the glomerular capillaries and is always mingled with hematoxylin-stained bodies. Its chemical nature and origin are therefore most likely the same. The conclusion is then warranted that the vascular fibrinoid in systemic lupus erythematosus is the product of

was originally proposed because pathologic-anatomic observations had convinced us that in certain maladies generalized alterations of the intercellular substances were the striking morphologic features and therefore of pathogenetic significance. Rheumatic fever belonged to this group, as well as polyarteritis nodosa among the diseases of the cardiovascular system (Klinge) (26) But our attention was drawn to the intercellular substances of the connective tissue by histologic investigations of systemic lupus erythematosus (27). Because cardiovascular alterations are very common in this disease it might be permissible to refer to observations in this malady to illustrate the role of the connective tissue in cardiovascular diseases. We were first impressed by widespread fibrinoid alterations of this tissue and, according to prevailing opinion, we considered them as an alteration of the collagen fibers. This was erroneous and in subsequent reports I have avoided reference to the collagen fibers as the seat of the connective tissue alteration My own observations agree with the findings of Altshuler and Angevine (28) that the fibrinoid material is deposited between the collagen fibers within the ground substance Fibrinoid connective tissue damage has been prominently featured by Klinge as a significant lesion in rheumatic fever. In fact it has been singled out by him for his pathogenetic interpretation. The occurrence of similar connective tissue changes in hypersensitive animals led him to the biologic-anatomic synthesis that maladies anatomically distinguished by fibrinoid connective tissue damage were of allergic background. This hypothesis has found widest acceptance all over the world, it has been championed by Rich (29) in this country. We did not agree with the sweeping generalization I have repeatedly detailed the reasons for our disagreement (30) But one of the reasons which I should like to emphasize was my doubt in the identity of the materials called fibrinoid which were found in so many heterogeneous diseases. In 1947 in a lecture (31) at this Academy I concluded that "it still seems necessary to inquire whether the apparent identity of fibrinoid collagen in such heterogeneous situations might not be a delusion "

It is generally agreed upon that fibrinoid connective tissue change is one of the conspicuous features of the pathologic-anatomic picture of systemic lupus erythematosus. For years I have attempted to identify this material. In 1941 we (27) demonstrated that the glomerular wire loops and the hyaline thrombi within their lumen which stain identically

were digested by trypsin This proved first that they were of proteinic nature but not identical with collagen. In later years Dr. Feitelberg of our Physics Laboratory by wide angle x-ray diffraction examined endocardial vegetations in this disease which, we believed, originate from intravalvular fibrinoid deposits. It was shown that they did not contain collagen, the x-ray diffraction pattern was that of a mixture of proteins but not characteristic Recent investigations, carried out by Drs. Gueft and Laufer (32) at Mount Sinai, and the Fairfield State Hospital, have thrown light upon the origin and nature of the fibrinoid substance deposited within the wall of glomerular capillaries and of arteries. These studies took their origin from our old observations (33) of hyaline thrombi within the glomerular capillary lumen and our recent analysis of the hematoxylin bodies (34). It was noted that some of the homogeneous eosinophilic plugs showed smudged particles stained with hematoxylin These particles were Feulgen positive and could therefore be identified as desoxyribose nucleic acid. It was thus suggested that they were the remnants of a progressive depolymerization of the DNA and that the major part of the hyaline thrombi consisted of the protein moiety of the nucleoprotein In order to test these deductions appropriate histochemical determinations were carried out. The hyaline thrombi and wire loops are digested by trypsin, they are Millon positive, strongly absorbing the light of a mercury vapor lamp of 3650 A wave length This proves the presence of tyrosin containing protein. The non-histone protein is such a compound According to White (35) histone stains strongly with orange G if submerged in a mixture of aniline blue and orange G at pH 3. The hyaline thrombi and wire loops stain selectively yellow under such circumstances. The results of the histochemical studies therefore support the assumption that the hyaline thrombi are the products of a progressive degradation of nucleoprotein of which the hematoxylin bodies represent an earlier phase Since the wire loops stain identically with the hyaline thrombi within the capillary lumen the conclusion seems justified that they consist of the same material which has impregnated the basement membrane. The fibrinoid of larger vessels is tinctorially identical with that of the glomerular capillaries and is always mingled with hematoxylin-stained bodies Its chemical nature and origin are therefore most likely the same The conclusion is then warranted that the vascular fibrinoid in systemic lupus erythematosus is the product of

the peculiar disturbance of nucleic acid metabolism which is, according to our studies, specific for the malady.

These observations further indicate that the connective tissue changes, commonly designated as fibrinoid, must not be considered to be of identical nature. It is evident that the fibrinoid alteration in systemic lupus erythematosus, which is the product of a pathogenetic mechanism specific of the malady, cannot be identified with fibrinoid connective tissue changes in other diseases in which this mechanism is absent, although the inadequacy of our conventional histopathologic technique and method of investigation suggests similarity. The popular generalization that fibrinoid alterations of connective tissue denote hypersensitivity is challenged by our observations just as much as the more recent generalization of a hyalinosis or collagen disease syndrome due to hormonal imbalance

In my introductory remarks I have referred to the uncertainty which still prevails in regard to the problem of the origin and source of the intermediate substances of the normal connective tissue. The fibrinoid substance plays an important role in the pathologic-anatomic definition of the so-called collagen diseases, and many of the maladies which can be included in this collective group are characterized by cardiovascular implication. Fibrinoid certainly is an abnormal component of the intermediate substances of the connective tissue. Its derivation from collagen fibers has become very doubtful indeed. One of the principal results of our recent studies of systemic lupus erythematosus is not only the recognition of its specific nature in this disease but also that it is derived from degradation products of nucleoproteins which are circulating within the blood. This relation between abnormal constituents of the blood plasma and vascular connective tissue changes seems to me of more general significance and worthy of further investigations.

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Chapter 2

CONTRACTION IN THE HEART MUSCLE FIBER *

A. Szent-Györgyi †

MUSCLE has two functions it shortens and creates tension. The two functions are, in their essence, but one, because one and the same change will produce contraction or tension according to conditions. If the ends of the system are free, it shortens. If they are fixed, they develop tension. Tension means that the contraction would occur with a certain force.

In order to create a system which could do all this Nature had to solve a number of problems of molecular engineering which we will discuss in succession

In order to build a system which can shorten, Nature had to use thin and long protein particles Thin and long particles always tend to fold up, thus shorten, especially if they are very small and are exposed to the bombardment of water molecules moved by heat-agitation. The thread-like, very thin and long protein particles, out of which Nature has built the contractile matter, is "*myosin.*"

If the myosin particle tends to fold up anyway then the first question we have to answer is not how it shortens but what keeps it straight in resting muscle There must be repulsive forces which repel, so to say, one end of the particle from the other Such repulsive forces are always electric coulombic charges. The myosin molecule generates its charges by dissociation Like other proteins, it has dissociating acidic and alkaline groups On dissociation the acidic groups acquire a negative, the alkaline groups a positive charge. The number of acidic groups is

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slightly greater than that of the alkaline ones, and consequently the myosin molecule has a negative net-charge.

This negative net-charge repels other equally charged protein particles Looking, however, closer into these relations we find that it is not the net negative charge which keeps other particles away. The negative charges are balanced by positive K+ ions which surround the particle They would actually remain in the closest proximity to the negatively charged particle, would heat-agitation not drive them away, as a wind whirls up dust It cannot drive them away altogether because this is not permitted by the electric attraction. The end result is that the myosin particle is surrounded by a cloud of positive K+ ions, thus a positively charged atmosphere, and if another myosin particle approaches it will be these positively charged atmospheres which meet first and repel one another, and thus keep the myosin in solution This atmosphere will also have the tendency to expand because the positive ions in it repel one another. The end result will be that not only other particles are kept away but the particles will be kept straight, extended.

How strongly this positive ionic atmosphere will repel other similar structures depends chiefly on two factors. First· the number of charges. The number of positive charges in this atmosphere is equal to the number of the net negative charges of the particle itself. Second· the thickness of this positive ionic layer. If the K-ions get very close to the particle then this latter's negative charges neutralize this outward effect. The ionic atmosphere will still be there and keep the particle straight but will not repel other particles any more, which now can approach the myosin particle. Colloidal particles always tend to approach and stick together owing to the Van der Waals cohesive forces and so, if coulombic repulsions do not drive them apart, they approach, stick together, and the final result is the formation of flocculi which rapidly settle to the bottom, i.e., precipitate.

I am not losing my way in intricacies of colloidal chemistry. These problems are most important for the contraction of the muscle fiber, be it heart or body muscle. This will be evident if we discuss the second problem of molecular engineering Nature had to solve when creating the muscle In resting muscle the myosin particle had to be kept straight, and we have seen how this is done. The next problem is how this particle can be made to contract not at a moment's but at a thousandth second's

notice How can all these charges be taken away within sigmas? There is one method known to all of you by which a protein can be discharged, that is precipitated (since precipitation is the expression of such discharge), and this is. by adding another specifically built protein, a precipitin Nature keeps in muscle such a precipitin for myosin. This protein has been discovered in my laboratory and is called actin. If an actin and a myosin particle meet in presence of a physiological salt concentration they unite to a complex actomyosin which becomes partly discharged. This discharge is a very involved process and the ions of the solution are involved in the reaction too. Here we are interested only in the end result The trick, applied thus by Nature, by which it produces the sudden folding of the myosin particle at a sigma's notice is to keep another protein, actin, at its side. The two proteins, in resting muscle, are separated by those repulsive forces we discussed before. The repulsive and attractive forces are carefully balanced, so to say, at the razor's edge. This balance is disturbed by the wave of depolarization which travels along the membrane and is called by physiologists "excitation" As a consequence of this disturbance actin and myosin get together and interact

The next problem which had to be solved concerns energy-relations· how to make these into a powerful machine. If our muscle lifts a weight it does work If a system does outside work it has to lose an equivalent amount of energy itself its free-energy content decreases If a great amount of work has to be done, as is the case in muscle, the system must lose a great amount of free energy There must be thus a great difference in the energy-content of the two states of actomyosin, the uncontracted, resting, high-energy state and the contracted low-energy state. Myosin itself, together with actin, is unable to produce two such states with such a great difference in energy-content Accordingly the contraction of which actomyosin is capable is very poor, the discharge very incomplete. Here comes ATP into the picture, that amazing substance which is in the center of cell-life and its energy changes Muscle contains ATP (adenosine-triphosphate) in relatively high concentration It is linked to the myosin by adsorption It is actually not myosin which unites with actin, but a myosin-ATP complex If this complex unites with actin to actomyosin-ATP we get a new substance which has two possible states, which differ greatly in energy content and physical appearance. The one

state is similar to the ATP-free actomyosin, with straight and highly charged particles while in the other state the particles are completely discharged, maximally folded. This state contains much less free energy. Every physical system tends to go into the state in which it contains the least energy, so if this actomyosin-ATP is formed in muscle under the influence of excitation it spontaneously goes over into its energy-poor contracted state. The loss of energy can be used to lift a weight, do work, or develop tension.

Now comes the last engineering problem which concerns relaxation, the return of the system into its original resting state.

The first law of thermodynamics tells us that, in relation to energy, we cannot get something for nothing So if the muscle has done work, has spent free energy in its contraction, it cannot return to its high-energy resting state without paying for the expense, that is to say, without liberating an equivalent amount of chemical, bound energy. This problem is solved by Nature by smuggling, so to say, energy into the ATP molecule When the ATP molecule is constructed and its phosphate groups are linked together, energy has to be invested to establish such links. This energy is released again when the link is split. The myosin has the ability to split this link, act as ATP-ase, and release the chemical bound energy which puts the energy-balance right, makes debit and credit side of the account tally again

From the point of view of muscular contraction the metabolic apparatus is nothing but a factory for ATP or more precisely a factory of high-energy-phosphate bonds. The metabolic apparatus releases the energy of foodstuffs and makes out of it ATP or some other form of high-energy-phosphate to replace by it the high-energy-phosphate links split in muscular contraction

You have certainly noticed I mentioned ions at every turn. They play an important role in all happenings It is the intracellular ionic atmosphere which decides the charges, the balance of repulsive and attractive forces, equilibrium-distances, the trend of actin and myosin to part or to get together, and, last but not least, decides also the tension developed in contraction—the development of tension, being also intimately connected with the distribution of charges, is governed by ions. It follows without saying that the regulation of the intracellular ionic atmosphere is one of the most important points in cell-life. At the same

time it is one of the most difficult problems. What makes it so difficult is the fact that this atmosphere cannot be kept constant, for it changes when the fiber is working. Every contraction, thus every heartbeat, disturbs it. At rest there is a high K-concentration and a low Na-concentration inside the fiber. Here, inside the fiber, the K-ions are linked to the protein by electrostatic attractions. The membrane itself is impermeable to Na When the wave of excitement depolarizes the membrane, the membrane becomes permeable to all ions and at the same time the charge-system of actomyosin collapses, which causes the K-ions to become entirely free They can now diffuse away through the depolarized membrane according to the gradient of their concentration, and the cell loses potassium In the next instant, however, the membrane is recharged, but meanwhile the fiber has lost K and we have a new ionic balance inside with less K. It takes time until the original balance is re-established The next contraction, if it follows soon, finds a changed ionic balance The cell is thus faced with the problem how to build its actomyosin should this actomyosin be constructed in such a way as to be capable of exerting its maximal tension at the resting ionic balance or at the balance which is found immediately after contraction The heart has to work with permanent rhythmicity beat follows beat. The ionic balance depends thus on the time-interval which elapsed since the preceding one, that is, it depends on the frequency It is natural, then, that the actomyosin should be built in such a way that it works well at the ionic balance which is found soon after a beat and should work poorly at the balance which will be found after a longer pause.

These relations are beautifully demonstrated by a phenomenon discovered eighty years ago by an American physiologist, Bowditch. Bowditch, working on the isolated frog heart, found that if the heart is arrested for some time, say for a few seconds, the first beat after this pause is weaker than the last one preceding it If a second beat was made to follow soon it was somewhat stronger The heart thus gradually regained its strength The gradual increase of the height of contraction was summed up by Bowditch under the name of "*staircase*"

We can now interpret this phenomenon and say that a beat leaves a decreased K-ion concentration behind which favors contraction If a longer pause occurs this favorable condition deteriorates The heart accumulates too much potassium, and the beat following the longer pause

finds an unfavorable ionic balance and needs a number of beats following one another in more rapid succession to re-establish the favorable charge-distribution again.

Dr. Hajdu and myself studied this phenomenon some time ago. We could fully corroborate Bowditch but also found that if we replace the Ringer's solution in our cannula by serum, we could stop the heart for a longer period and the next beat after this pause was just as good as the last before it. There was no staircase or only a very mild one. We were thus able to conclude that serum contains a substance which eliminates the staircase and renders the membrane relatively impermeable to the potassium thrown out during contraction, and enabled the heart to maintain the favorable condition, following contraction, for a longer period. As chemists, naturally, we wondered what this substance in serum could be. We found it to belong to the sterols. Desoxycosterone had such an action which seemed to have a high degree of specificity. Of the number of sterols tested only the closely related progesterone had a similar action, as was found in experiments in which Dr. Oscar Hechter from the Worcester Institute for Experimental Biology came to our help We found only one other group of substances which had a similar action, and this was the closely related group of digitalis. Digitoxin and all the related heart glycosides produced such an action. These substances are one of the best friends of man, which come to his help when his heart begins to fail. This indicated that the staircase has far-reaching pathological importance. When the heart is damaged it seems to be unable to keep the potassium out. Whether the heart lacks the regulating sterols which help to keep the K out or is merely unable to bind these sterols, we do not know. What we know is that we can come to its help with digitalis which keeps the ionic balance right.

When a heart becomes insufficient the pulse rate goes up. This is probably the only way in *which the heart can maintain* a favorable K-balance. If it would beat more slowly the pauses would be too long for the damaged permeability, and, similarly to the Bowditch experiment, the beats would become poorer and poorer and a vicious circle would be established. The only way out is to beat fast, let one beat follow the other in order to keep the intracellular [K] at the lower level. However, by doing so the heart finds itself, if I may say so, between the devil and the deep blue se · b ·reducing the period of rest it has less time for

recovery, while by extending it it develops a downgrade staircase. It is here that the balance is put right by digitalis, which allows the heart to beat slowly without losing its strength. This is probably why one of the first symptoms of a digitalis therapy is the slowing of the heart rate.

What happens in many pathological processes seems to be analogous to what we see in the perfused frog heart: the freshly isolated frog heart is well provided with the regulatory substances and develops a high tension at all frequencies. At the point at which its membrane loses its regulatory substances the staircase develops, and we have to increase the frequency gradually to maintain maximal tension. Eventually the heart fails, having no time for recovery. We can now put things right by digitalis which replaces the normal regulatory substances and allows the heart to beat *slowly* and *strongly* again. Concomitant with this change there is also a change in the whole form of the heartbeat. If we register it on the smoked drum, we see that the diastole develops more slowly, the descending slope of the curve becomes flatter. This indicates that actin and myosin part less readily, have a tendency to get and stay together, the ionic balance having been changed in such a way as to increase the mutual attraction between the two proteins. If this effect is exaggerated by an excessive dose of digitalis, actin and myosin will be unable to part at all and contracture develops.

To conclude, let us sum up events once more in their natural sequence. There is no essential difference between heart and body muscle as far as the mechanism of contraction itself is concerned. There is, however, an essential difference in the mode in which the excitation is generated. In the body muscle excitation is produced in the nerve ending by messages coming from the central nervous system. The heart muscle has no such innervation and has to generate its excitation itself. This excitation, that is, the depolarization of the membrane, is generated at a preferential point close to the sinus, but every point is capable to do the same only at a slower rate so that the pace, under normal conditions, is dictated by the sinus node. The membrane is built in such a way that the depolarization generated here becomes self-propagatory and runs through the whole length of the fiber membrane. In its wake the distribution of charges is disturbed and brings actin and myosin together. How the depolarization actually does this we do not know. Z. Bay and myself showed that the wave of depolarization produces an electric field inside the fiber, parallel

to its axis, but we were unable to show yet conclusively that it is this "window field" which transmits the excitation of the membrane to actomyosin. The membrane, however, not only produces, propagates, and transmits excitation: at the same time it also regulates by its specific permeability the intracellular ionic atmosphere which decides the whole issue. Once actin and myosin have united they contract with the aid of ATP, which by its splitting and rephosphorylation causes muscle to relax. If the membrane is repolarized, ATP rephosphorylated, we have the same condition as we had in resting muscle and actomyosin dissociates into actin and myosin. The latter stretches out and the muscle is at rest again; everything is set for a new contraction. At the side of this machinery is the metabolic apparatus which replaces the split high-energy-phosphate bonds.

In the analyses of a pathological condition the first question, which has to be answered is, which part of this complex machinery is out of order? This question has not been answered yet for most diseases of muscle tissue. The reason is evident. Our ignorance of muscle is still very dense, and we do not know the single processes involved in contraction, sufficiently yet. So, for instance, we have practically no notion of the chemical mechanism of excitation, we only know that ATP here too plays a central role. With the discovery of actin and actomyosin and its amazing reactions with ATP a solid basis is created for the study of these problems which represent one of the newest and almost virgin fields of scientific inquiry.

LIPID METABOLISM AND ATHEROSCLEROSIS *

Aaron Kellner †

ARTERIOSCLEROSIS has until quite recently been regarded in the same frame of reference as the phenomena of aging, the implicit assumption being made that just as all living creatures pass inevitably from a period of growth and maturation into one of senility and decay, so too the vascular channels harden and wear out (1). Hence, the degenerative changes in blood vessels came to be looked upon as the natural and inexorable sequelae of life, the price that human tissue paid for prolonged survival. Indeed, the acceptance of arteriosclerosis as a natural process, susceptible to neither remedy nor prophylactic, was for many years responsible for retarding fruitful investigations into its etiology and pathogenesis. It was not until the third and fourth decades of the present century that it became increasingly plain from clinical, morphological, and experimental observations that arteriosclerosis constituted more than a single morbid process, and, furthermore, that its most serious manifestations were not essential concomitants of aging (1, 2) but represented rather an acquired abnormality, in Aschoff's words, a disease process "superadded to the process of aging" (3). This change in concept was an important one, for it came at a time when the infectious diseases had in large part been mastered and when diseases of the heart and blood vessels were becoming foremost among the afflictions of mankind, and it was soon to have a stimulating influence on thought and experiment in the field of vascular disease.

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Nosological and Morphological Considerations

The imperfections of nomenclature have often proved a source of confusion and irritation in medicine, and to this term arteriosclerosis is no exception. Coined by Lobstein in 1833, it is a generic term applied to a group of vascular diseases characterized morphologically by hardening of the vessel wall, and includes such heterogeneous conditions as atherosclerosis, Monckeberg's or medial sclerosis, arteriolosclerosis, and the *age-changes that do occur in* blood vessels In addition *to embracing* a diversity of clinical and pathological states, the term arteriosclerosis lays undue emphasis upon the hardening aspect, a feature that is scarcely an adequate criterion for estimating the severity of change within the artery wall, for hardening per se is a relatively benign process which produces little if any interference with the flow of blood Thus, for example, Mönckeberg's sclerosis which leads to widespread and often confluent calcification of the media, particularly in the extremities, rarely impinges upon the caliber of the lumen unless it is complicated by other processes. Likewise, the changes that occur with age in the walls of blood vessels (and blood vessels like other tissues are susceptible in some measure to the ravages of time) consist primarily of loss of elasticity with resultant dilation and tortuosity (4, 5), a phenomenon *that is plain for* all to see in the corkscrew temporal arteries exhibited by many individuals past the age of forty, and one that does not compromise the lumen or embarrass the flow of blood. Atherosclerosis, on the other hand, is vastly more serious, for it is characterized not so much by hardening of the vessel wall as by narrowing or obliteration of the lumen This is an occlusive disease that affects the nutrient vessels of the heart or brain or kidney, and, by progressively choking off the flow of blood, leads to functional alteration and, all too commonly, to disability and death. It is with atherosclerosis that we will be concerned in the ensuing presentation

In the absence of more precise knowledge of its etiology and pathogenesis, *atherosclerosis* is for the present best defined in morphological terms, its distinctive and fundamental feature being the presence of stainable lipid within the lesion. The earliest recognizable lesions of atherosclerosis, of which the fatty flecks or streaks commonly present in the aorta even in childhood are a typical example, are made up of

small focal collections of lipid, sometimes free though usually in foamy macrophages, just beneath the endothelium. These minute intimal cushions project only slightly into the lumen, and offer little or no hindrance to the flow of blood, indeed, they may at this stage even be reversible. It is noteworthy that the endothelium overlying the area of initial involvement is almost always structurally intact—a fact that speaks strongly against the hypothesis that injury to the intima is the primary pathogenetic event. As the process continues, the lesions increase progressively in size and number and often coalesce to form large lipid-rich intimal plaques that gradually begin to encroach upon the lumen With expansion of the lesions the foam cells in their depths undergo necrosis and disintegrate, discharging their lipid and cellular debris to convert the central portion into a soft, pultaceous mass—the atheroma from which the entire process derives its name. In time, secondary changes become manifest, prominent among which are thickening of the overlying endothelium, disruption of the elastica with invasion of the media, fibrosis, hyalinization, and calcification. Continued enlargement of the lesions leads eventually to serious diminution in the caliber of the lumen, especially in the relatively narrow vessels of the heart and brain, and slowly throttles the flow of blood through these vital channels Not infrequently, the flow of blood in atherosclerotic vessels, particularly in the coronary arteries, may be halted more abruptly by thrombosis or by hemorrhage into an atheromatous area. These latter events, however, dramatic and lethal though they be, are but complications in the evolution of atherosclerosis It is to the early and basic lesion—the infiltration of lipids into the intima—that we must turn for clues to the secrets of this morbid process.

Biological and Historical Considerations

Before examining the factors currently thought to be implicated in the causation of atherosclerosis, it would be useful in attaining perspective to touch briefly upon some features of the natural history of this disease. One biological aspect of atherosclerosis that deserves more consideration than it usually receives is the remarkable fact that man is the only mammal in which the disease occurs regularly to any significant degree. To be sure, wild animals in their natural habitat seldom live to old age and consequently might not be expected to manifest

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tensions of modern life contribute heavily to the causation of atherosclerosis, it would seem that the builders of the pyramids were in their time as much a prey to anxieties and tensions as are the splitters of the atom today (9)

It is relevant to inquire whether such factors as race, age, or sex influence man's susceptibility to atherosclerosis. The question of racial differences cannot be answered definitely at the present time. Atherosclerosis is said to be a relatively mild and infrequent disease amongst certain Oriental peoples, the Chinese and Okinawans for example, and attempts have been made to correlate the observation with hereditary or dietary factors, the low consumption of fat and cholesterol-containing foods among those peoples being the distinction most often stressed (10, 11). The data, however, must be scrutinized with care, since vital statistics in those countries are incomplete and not entirely reliable, and, also, since the average life expectancy in those lands is so much shorter than it is in Western countries that figures for the incidence of diseases such as atherosclerosis and cancer, which require many years for their full development, are not really comparable. The evidence, therefore, for the existence of important racial differences must be regarded for the moment as not completely convincing. The role of heredity, on the other hand, has been well substantiated. For the extensive family studies of Wilkinson (12) and of Adlersberg (13) have demonstrated the existence of fairly common genetically transmitted abnormalities of lipid metabolism that are associated with the frequent and early development of clinical atherosclerosis, and, conversely, it is well known that there are families that are singularly long-lived and relatively free from the disease

The part played by age in the genesis of atherosclerosis has been much discussed. It is now generally agreed that though atherosclerosis is not a necessary result of "the wear and tear of life," it is indirectly related to the aging process in the sense that it is a cumulative and slowly progressive disease that becomes increasingly manifest with the passage of time The lesions of atherosclerosis are frequently encountered early in childhood and, as a rule, their extent and severity become more prominent with advancing age Though virtually no one is completely free from the mark of the disease, it is, nevertheless, striking to observe on occasion how slight may be the degree of atherosclerosis even in

extensive atherosclerosis. Many animals, however, have been permitted to live their full life span in scientific laboratories and zoological gardens; furthermore, a great many of them have been carefully examined post mortem, one of the noteworthy studies in this connection being the 10,000 autopsies performed in the Philadelphia Zoo (6). Analysis of this post-mortem data by Herbert Fox reveals that while medial calcification is frequently encountered in the arteries of various mammals, the lesions of atherosclerosis are exceedingly rare, indeed, clinically significant atherosclerosis is virtually absent. Birds, on the other hand, not infrequently do exhibit considerable atherosclerosis, although the lesions are seldom of sufficient severity to produce symptoms or to cause death. This paucity of significant naturally occurring atherosclerosis among animals stands in striking contrast to the extraordinary incidence of the disease in man, and provides a challenge for incisive thought and experiment to bring to light the metabolic or perhaps environmental factors that may be involved.

Since atherosclerosis as a serious and fatal disease appears to be limited to the human species, the question then arises whether it is a relatively new disease attacking man in our modern society or whether it has been an affliction of mankind from the days of antiquity. In the case of most diseases the answer to such a question would hinge upon the interpretation of a reference in Scripture or ancient legend; in the case of atherosclerosis, however, a clear answer is provided in one of the most intriguing chapters in the history of medicine. Some 40 years ago archeologists working in the valley of the Nile unearthed hundreds of mummies dating back more than 1500 years before the Christian era, and many of these were in such an excellent state of preservation, due to the favorable influences of a dry climate and the embalming procedures practised by the ancient Egyptians, that it was possible to remove portions of the aorta and other major vessels and to prepare remarkably good histological sections from them. Extensive studies of the arterial lesions of Egyptian mummies by Ruffer (7) and by Shattock (8) make it plain that atherosclerosis was a very common disease 3000 and more years ago and that the morphological character of the lesions, their distribution, and severity differed in no way from those seen post mortem today. Man, it appears, has been a victim of atherosclerosis for thousands of years; and if, as some think, the anxieties and

important, the production of atherosclerosis in animals by experimental procedures that disturb their lipid balance.

It was appreciated by Virchow almost a century ago on morphological grounds that lipids are a prominent constituent of atheromatous plaques (16). More precise chemical studies by Windaus (17), Schonheimer (18), and others (19, 20) have since shown that the lesions of atherosclerosis are rich in cholesterol and cholesterol esters, while containing in addition an admixture of other lipids, notably phospholipids and neutral fat. Indeed, the lipid composition of early atheromatous plaques is so similar to that of blood plasma as to suggest that the atheromatous lipids are in fact derived from the plasma. There was, however, no direct confirmation of this view until quite recently, when it was demonstrated that radioactive cholesterol administered to animals can be detected in the atheromatous foci (21), and, further, by studies which show that under normal conditions the endothelium is permeable to a considerable portion of the plasma lipids (22). The concept that plasma lipids stream through the endothelium and, under certain conditions to be discussed presently, leave behind a fatty sludge is a basic one in present-day understanding of the pathogenesis of atherosclerosis, and has been aptly and colorfully termed the "delta theory" (23).

Clinicians have long sensed that there is some causal connection between lipid metabolism and atherosclerosis because of the frequent observation that patients with diabetes, xanthomatosis, hypothyroidism, and nephrosis, who exhibit marked hypercholesterolemia, are prone to develop severe atherosclerosis and often at a relatively early age. Moreover, study of selected groups of patients with coronary occlusion and myocardial infarction reveal that in general they have blood cholesterol levels that are considerably higher than the normal, and, also, that the cholesterol levels of such individuals tend to fluctuate between wider than normal limits (24, 25). On the other hand, the picture is blurred by the fact that the vast majority of people presumably developing atherosclerosis have blood cholesterol levels that fall within the accepted normal range. Indeed, numerous investigations have been unable to demonstrate that an elevated blood cholesterol level is an essential prerequisite to the development of atherosclerosis (26, 27, 28). The normal range of blood cholesterol, too, has been, and to an extent still is, a much debated ques-

extremely aged individuals. The almost universal prevalence of the disease, coupled with the fact that advanced calcified and eroded lesions are regularly encountered in association with fresh, soft, lipid-rich lesions has led to the concept of atherosclerosis as an episodic disease (14). Thus, at irregular intervals throughout life, if the proper conditions are present (and they appear to be present to some extent in most of us), clusters of lesions are formed which then slowly undergo degenerative or perhaps even some retrogressive changes, to be followed at some future date by a repetition of the cycle, so that at the end of life there is revealed to the pathologist's eye as an end result the sum total of these additive insults to the vascular tree.

When compared with the male, the female of the human species leads a charmed life with respect to atherosclerosis. Serious coronary artery disease, for example, is remarkably rare in females under age 40, though it is not at all uncommon in the young male, and the decreased susceptibility of the female to the disease is maintained consistently even in the later decades of life, but to a somewhat lesser degree. This freedom from atherosclerosis enjoyed by females is, of course, only a relative one, for they do develop atheromata that are identical in morphology and location to those seen in the male, but at each age level the severity of the lesions in the female, as well as the clinical consequences thereof, are distinctly less marked (15). It is only when they suffer from diabetes or hypertension that females manifest a degree of atherosclerosis comparable to that of the male. It may be noted, parenthetically, that the advantage possessed by the "weaker" sex with regard to atherosclerosis is in large measure responsible for the fact that as a group they can look forward to decidedly greater longevity than males.

Lipids in Atherosclerosis

The concept that atherosclerosis is fundamentally a disorder of lipid metabolism derives from several sources: first, the demonstration by morphological and chemical means that the lesions themselves contain abundant lipid, second, the oft-made clinical observation that disease states characterized by abnormally high blood lipids are frequently associated with premature atherosclerosis, and, third, and perhaps most

supplementary cholesterol to the diet; and, subsequently, Kendall and his associates (33) produced atherosclerosis in the dog, a carnivorous animal, by suppressing thyroid function with thiouracil and adding cholesterol to the diet. Furthermore, recent studies employing isotopic tracers have demonstrated beyond doubt that, herbivorous though they be, rabbits are capable of synthesizing and metabolizing large quantities of cholesterol (21, 34). It would appear from the accumulated evidence, therefore, that the cholesterol-induced arterial lesions in rabbits, and also those in the chick and the dog, while perhaps not precise counterparts of the atherosclerosis of human beings, are nevertheless so similar as to suggest the operation of closely allied, if not identical, pathogenetic factors Yet the mechanism whereby cholesterol feeding induces atherosclerosis in the experimental animal remains undisclosed, and a number of facts make it seem doubtful that elevated blood cholesterol is alone responsible for the development of the disease (35).

At this point we must digress momentarily to survey the rapid advances in lipid chemistry made possible quite recently by the availability of elegant new tools and techniques—heavy water, radioactive isotopes, electrophoresis, and the ultracentrifuge, to mention but a few It has become apparent that cholesterol, once considered to be chemically inert and metabolically inactive, is an essential constituent of the mammalian cell and an extremely active metabolite. The evidence is now clear that many tissues can synthesize cholesterol both in vivo and in vitro from simple and readily available precursors such as acetate radicals (29, 36), that there is a surprisingly rapid interchange between the cholesterol of plasma and that of the liver and other tissues (29); and, also, that the organism as a whole has metabolic facilities not alone for excreting but also for breaking down the cholesterol molecule (37). It is estimated that human beings may synthesize as much as 1500 to 2000 mg of cholesterol per day (29), an amount, it is worth noting, far in excess of the average dietary intake Similarly, evidence is now at hand for synthesis and active metabolism of the phospholipids and fatty acids, though it would take us far afield to catalogue in detail these and other impressive advances in lipid chemistry.

One area of investigation, however, concerned with the question of lipid transport, is germane to our central theme, for the progress made in this field quickly enriched our understanding of atherosclerosis. A

tion. In most clinical laboratories the normal figures usually cluster about 200 mg/100 cc, though some workers regard levels up to 350 mg/100 cc as being within the normal span. In this connection, Gould (29) has pointedly observed that, when compared to the very much lower levels for blood cholesterol normally present in most animals, even a figure of 200 mg may be considered excessive, and he puts forward the disturbing suggestion that our so-called normal figures may actually represent a state of chronic hypercholesterolemia.

The evidence that atherosclerosis is causally related to a disturbance of lipid metabolism rests in large measure upon studies of the disease in experimental animals, notably those concerned with cholesterol-induced arterial lesions in rabbits, though in some quarters these studies have been unthinkingly maligned and their true significance minimized. In 1913 Anitschkow (30) made the startling discovery that if rabbits are fed 0.5 to 1 gm of cholesterol per day they soon manifest striking elevations of blood cholesterol, and, after some weeks, develop intimal lesions of the aorta and other major arteries that in morphology and lipid content bear a remarkable resemblance to the naturally occurring lesions encountered in human beings. To be sure, there are some differences between the experimentally induced disease in rabbits and that seen in man; these involve chiefly differences in distribution, the lesions being more prominent in the thoracic aorta and pulmonary artery in the rabbit, whereas in man the abdominal aorta is more severely affected and the pulmonary artery spared; and also the fact that the arterial lesions in the rabbit are almost invariably associated with sustained hypercholesterolemia and are usually preceded by the deposition of lipid in the reticuloendothelial system and other viscera (31). The major objection to these experiments is based on the assumption that the rabbit being a herbivorous animal lacks metabolic facilities to handle cholesterol, a substance normally foreign to its diet, and, consequently, when this foreign material is included in the diet, it is precipitated in various organs and blood vessels This cogent argument was utilized effectively by those who felt that observations made on atherosclerosis in rabbits were not transposable to the disease in human beings. During the past few years, however, the ground on which this objection was founded has been largely cut away In 1942, Dauber and Katz (32) succeeded in producing atherosclerosis in the chick, an omnivorous animal, by adding

supplementary cholesterol to the diet, and, subsequently, Kendall and his associates (33) produced atherosclerosis in the dog, a carnivorous animal, by suppressing thyroid function with thiouracil and adding cholesterol to the diet Furthermore, recent studies employing isotopic tracers have demonstrated beyond doubt that, herbivorous though they be, rabbits are capable of synthesizing and metabolizing large quantities of cholesterol (21, 34) It would appear from the accumulated evidence, therefore, that the cholesterol-induced arterial lesions in rabbits, and also those in the chick and the dog, while perhaps not precise counterparts of the atherosclerosis of human beings, are nevertheless so similar as to suggest the operation of closely allied, if not identical, pathogenetic factors. Yet the mechanism whereby cholesterol feeding induces atherosclerosis in the experimental animal remains undisclosed, and a number of facts make it seem doubtful that elevated blood cholesterol is alone responsible for the development of the disease (35).

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One area of investigation, however, concerned with the question of lipid transport, is germane to our central theme, for the progress made in this field quickly enriched our understanding of atherosclerosis A

problem that has long perplexed chemists and biologists is the mechanism whereby blood plasma, essentially an aqueous medium, can maintain in exquisitely clear solution so large a quantity of lipid, since there are normally in each 100 cc of plasma some 500–800 mg of cholesterol, cholesterol ester, phospholipid, and neutral fat—all compounds which in their pure state are virtually insoluble in aqueous media. Light has recently been thrown on this problem by the work of Boyd (38), confirmed and extended by Ahrens and Kunkel (39), which points to the phospholipids as being important in maintaining the stability of the plasma lipids; these workers have demonstrated that plasma remains clear even at abnormally high cholesterol and neutral fat concentrations so long as the phospholipids are concomitantly elevated, whereas the emulsion is unstable and the plasma appears milky if the relative phospholipid content is low. Still more recently, certain plasma proteins have been found to be intimately concerned in the process. This relationship was first hinted at by the imaginative studies of Macheboeuf (40); it has been enlarged and placed on a firm and quantitative basis by investigations made in the laboratories of Tiselius in Sweden (41) and Cohn in this country (42) From these studies it now seems probable that the bulk, if not all, of the plasma lipids are present in combination with protein. Indeed, Oncley and his co-workers (43) have elaborated chemical techniques for the separation of two lipoproteins from human plasma, identified electrophoretically as alpha and beta globulins, which between them contain almost all the plasma lipids, and, further, the beta-lipoprotein has been purified and found to be soluble in aqueous media despite the fact that it is composed largely of lipid How these important new facts concerning lipid transport bear upon the problem of atherosclerosis will appear as we scrutinize some recent observations made on the disease in experimental animals and in man.

It has been noted by several groups of workers (44, 45) that in normal rabbits the blood phospholipid level is usually somewhat higher than the cholesterol level, whereas in cholesterol-fed rabbits with atherosclerosis, this situation is reversed, the blood cholesterol level being regularly much higher than the phospholipid. In view of the part played by the phospholipids in stabilizing the serum lipid emulsion, it was suggested that this disparity between cholesterol and phospholipid might be an important factor in the development of experimental atherosclerosis A

means of testing this hypothesis became available when it was found that certain surface-active agents when injected intravenously produced, among other things, marked and sustained elevations of the blood phospholipid content (46). Accordingly, an experiment was performed in which rabbits fed a high-cholesterol diet were given repeated intravenous injections of the surface-active agents Tween 80 or Triton A-20. The injected animals developed far less atherosclerosis than did uninjected control animals fed the same cholesterol diet, and it is of interest that the degree of atherosclerosis could be correlated with the blood phospholipid level, the injected animals had high phospholipid as well as high cholesterol levels, in sharp contrast to the controls in which the cholesterol levels were comparably elevated but the phospholipid levels distinctly lower (47). Similar findings have now been reported by Duff and his colleagues (48), who also found that the protective effect of alloxan diabetes against the development of cholesterol-induced atherosclerosis in rabbits, previously discovered by them, could be correlated with elevated phospholipid and neutral fat levels (49). Moreover, the clinical studies dealing with blood phospholipids done by Ahrens (50) in patients with biliary obstruction, those of Gertler (51) in patients with coronary artery disease, and those of Eilert (52) in women receiving estrogenic hormone therapy, though not conclusive, do suggest that the cholesterol-phospholipid ratio may be a factor in the atherosclerosis of human beings as well These clinical and experimental findings serve to focus attention upon the physicochemical state of the blood lipids and upon the interrelations between the various lipids, rather than upon the absolute level of the blood cholesterol, as being important determinants involved in the pathogenesis of atherosclerosis.

During the past two years the picture has acquired more detail with the appearance of the ingenious and provocative studies of Gofman and his associates (53, 54). These investigators using the analytical ultracentrifuge found that all the major lipids in the serum are transported in the form of giant lipid-protein complexes which can be characterized and quantitated by their ultracentrifugal flotation properties. The pattern of these lipoprotein molecules, though differing widely from one individual to another, is quite constant under normal conditions for any one individual during prolonged periods of time, and is subject to modification by diet, disease, and certain drugs. While these complexes are more

common in hypercholesterolemic sera, they may, and very frequently do, occur in the sera of patients with normal or even low cholesterol levels. Further, these workers observed that one portion of the spectrum of these large lipoprotein aggregates, those classified in the Sf 10–30 category, are regularly associated with the development of experimental atherosclerosis in cholesterol-fed rabbits, and, similarly, the molecules in the Sf 12–20 range appear to bear a strong correlation to the development of the disease in human beings. Comparison of a large group of normals with a matched group who had suffered myocardial infarction reveals a significantly greater incidence of excessive concentrations of these abnormal molecules in the sera of the latter group. Moreover, these workers maintain that the level of Sf 12–20 molecules in the blood may serve to designate, years in advance of its clinical manifestations, those who are susceptible to severe atherosclerosis, and may be useful as a means of estimating prognosis and evaluating therapy following myocardial infarction. It is noteworthy that females, especially in the early and middle-age groups, have in their sera far lower concentrations of these molecules than do males, a fact which may account for their relative freedom from clinical atherosclerosis. Graham, working in Gofman's laboratory, has recently reported (54) that injection of heparin into human beings and experimental animals brings about a dramatic reversal toward normality in the serum lipoprotein picture, and that repeated injections into rabbits protect them against the atherosclerosis of cholesterol feeding. It is of interest that the effect of heparin is apparently unrelated to its anticoagulant action. This intriguing observation, quite apart from its possible therapeutic implications, may provide a clue to understanding the metabolic relations involved in the formation of lipoprotein complexes. Despite the recognized difficulties of quantitating atherosclerosis in human beings—for neither clinical, radiographic, nor even post-mortem estimates are wholly reliable—and despite the acknowledged pitfalls in finding an adequate control series for a disease which is practically universal, it must be stated that the association between the serum concentration of these large lipoprotein molecules and the development of severe atherosclerosis is more impressive than any that has hitherto been demonstrated. Whether these molecules are themselves the offending agent in atherosclerosis or whether they represent an epiphenomenon, a reflection of a more ultimate cause, remains to

be determined It is nevertheless becoming increasingly clear from these researches, and from the parallel studies of Barr, Russ, and Eder (55) using chemical techniques to fractionate plasma lipoproteins, that in atherosclerosis there is an underlying lipid metabolic defect, one of the manifestations of which is an aberration of lipid transport which appears to promote the deposition of lipid within the intima of blood vessels.

Attention has been drawn for a long time to the possible role of dietary factors in the causation of atherosclerosis The question has frequently been raised whether overabundant diet, rich in fatty and cholesterol-bearing foods, may not be responsible for the alarming incidence of atherosclerosis in our society. In brief, are we eating our way to atherosclerosis? A decisive answer to this question is not forthcoming at the present time The post-mortem studies of Wilens (56) and the experimental observations of Firstbrook (57) point to a correlation between *overnutrition* and atherosclerosis. The level of blood cholesterol, though little influenced by moderate fluctuations in the cholesterol or fat content of the diet (58), may be appreciably reduced by rigid restriction of both, as in the rice diet (59, 60) It is a curious fact, however, that addition of vegetable fat containing no cholesterol to such a severely curtailed diet causes a return of the blood cholesterol to previous levels, making it plain that elimination of cholesterol-containing foods from the diet is not effective unless the total fat content of the diet is stringently reduced at the same time (58, 61) It has been pertinently said of atherosclerosis that if cholesterol is the culprit, fat is an active accomplice (62). Gofman has studied the effect of diet on the lipid transport mechanism, and he has reported a decrease, and on occasion even disappearance, of the Sf 12–20 lipoprotein molecules from the blood of individuals placed on diets of low fat and low cholesterol content (54) Such diets have in fact been advocated as having beneficial effects in atherosclerosis, though the evidence for this is still quite incomplete. In connection with dietary factors one must consider the lipotropic agents, especially choline and inositol, which, because of demonstrated effectiveness in reversing the fatty liver of certain nutritional deficiencies and perhaps also because they are essential constituents of the major blood phospholipids, have been advocated and widely employed in the therapy of atherosclerosis (63) The results of clinical trials, however, are unconvincing, and the use of these agents in experimental animals has repeatedly been found un-

common in hypercholesterolemic sera, they may, and very frequently do, occur in the sera of patients with normal or even low cholesterol levels. Further, these workers observed that one portion of the spectrum of these large lipoprotein aggregates, those classified in the Sf 10-30 category, are regularly associated with the development of experimental atherosclerosis in cholesterol-fed rabbits, and, similarly, the molecules in the Sf 12–20 range appear to bear a strong correlation to the development of the disease in human beings. Comparison of a large group of normals with a matched group who had suffered myocardial infarction reveals a significantly greater incidence of excessive concentrations of these abnormal molecules in the sera of the latter group Moreover, these workers maintain that the level of Sf 12–20 molecules in the blood may serve to designate, years in advance of its clinical manifestations, those who are susceptible to severe atherosclerosis, and may be useful as a means of estimating prognosis and evaluating therapy following myocardial infarction. It is noteworthy that females, especially in the early and middle-age groups, have in their sera far lower concentrations of these molecules than do males, a fact which may account for their relative freedom from clinical atherosclerosis. Graham, working in Gofman's laboratory, has recently reported (54) that injection of heparin into human beings and experimental animals brings about a dramatic reversal toward normality in the serum lipoprotein picture, and that repeated injections into rabbits protect them against the atherosclerosis of cholesterol feeding. It is of interest that the effect of heparin is apparently unrelated to its anticoagulant action. This intriguing observation, quite apart from its possible therapeutic implications, may provide a clue to understanding the metabolic relations involved in the formation of lipoprotein complexes. Despite the recognized difficulties of quantitating atherosclerosis in human beings—for neither clinical, radiographic, nor even post-mortem estimates are wholly reliable—and despite the acknowledged pitfalls in finding an adequate control series for a disease which is practically universal, it must be stated that the association between the serum concentration of these large lipoprotein molecules and the development of severe atherosclerosis is more impressive than any that has hitherto been demonstrated. Whether these molecules are themselves the offending agent in atherosclerosis or whether they represent an epiphenomenon, a reflection of a more ultimate cause, remains to

fact that hypertensives, both male and female, are particularly susceptible to atherosclerosis and its more serious complications (71).

"Science," Conant (72) has stated, "advances not by the accumulation of new facts, . . but by the continuous development of new and fruitful concepts" Judged by this standard, substantial progress has been made in our understanding of atherosclerosis. The happenings of the past few years, herein briefly recounted, surely attest to the profound stirring that is now perceptible in this field Numerous investigators armed with wondrous new tools are probing deeply into the vital chemistries of tissues and cells An abundance of new facts has been wrested from nature, and based on them there have been erected dynamic and fruitful concepts that bode well for the future and hold much promise for clinician and experimentalist As a result of these advances, the attitude of hopelessness about the disease is giving way to one of quiet optimism that in atherosclerosis prevention and, indeed, even therapy may be attainable

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successful in raising blood phospholipid levels or in affecting appreciably the development or resorption of atherosclerosis (64, 65, 66). Thus, additional clinical and experimental data are required before the role of diet and specific dietary factors in this disease can be accurately assessed

Lest we become so preoccupied with the chemistry of lipids that we lose sight of the blood vessels where the disease actually strikes, mention must be made of the operation of other factors which, though perhaps ancillary, are nevertheless important in a full understanding of atherosclerosis as a pathological process. It seems quite probable from studies on the permeability of the endothelium that there is a constant flow of plasma filtrate containing lipids and many other substances across the endothelium into the interstices of the vessel wall (67), whence they are removed via lymphatics or vasa vasorum by mechanisms as yet undisclosed. Interference with these removal mechanisms may well account for the localization of atheromata at sites of injury to the vessel (68), and also at points of fixation and branching, and, in like manner, may explain the propensity of syphilis to enhance the severity of atherosclerosis in the thoracic aorta (69). Intravascular pressure is unquestionably another factor in the localization of atheromata, lesions being most common at points of high pressure and scarce or absent where pressure is low. Thus, the systemic arterial tree is most vulnerable, the pulmonary circulation distinctly less so except in instances of pulmonary hypertension, and the veins virtually unaffected by the disease, though, needless to say, the lipid composition of the plasma is essentially the same in all compartments of the arterial and venous channels. That increased blood pressure may also augment atherosclerosis has recently been demonstrated experimentally by Wakerlin (70). Dogs were made hypertensive by the Goldblatt technique and then fed a diet containing cholesterol and thiouracil, these animals developed atherosclerosis at a strikingly accelerated rate as compared with that of normotensive controls fed the same diet. It should be noted in this connection that dogs with sustained hypertension for many years do not develop atherosclerosis in the absence of the disturbed lipid metabolism induced by the diet The effect of pressure is thought to derive from increased filtration through the vessel wall, which, if the underlying lipid defect of atherosclerosis is present, serves to hasten the deposition of lipid. It may be that such a mechanism is responsible, in part at least, for the well-recognized clinical

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The Serum Lipid Factor in Atherosclerosis

In several publications (1, 2, 3, 4, 5), a group of us have described several lipoproteins in the serum of humans, certain of which lipoproteins are associated with atherosclerosis.* The developing studies of these lipoproteins now allow some systematization of lipoprotein interrelationships Our present concepts of such interrelationships will undoubtedly require modification and extension, but still are useful for orientation and the planning of further studies.

The lipoproteins to be found in human serum are characterized in general by having a density lower than that of such serum proteins as the albumins and globulins. Further the lipoproteins range in density from those as high as 1 12 gm/cc to some of less than 1.0 gm/cc. We have been studying the entire "spectrum" of such lipoproteins in the effort to understand lipid transport. For certain purposes, however, it is convenient (although arbitrary) to segregate the lipoproteins into two major subgroups by means of a cutting point at 1.063 gm/cc. Those lipoproteins of density less than 1 063 gm/cc we have referred to as the "low-density lipoproteins" If such lipoproteins are present in a salt solution of density 1 063 gm/cc, they will undergo flotation when placed in an ultracentrifugal field In the analytic ultracentrifuge such lipoproteins can be quantitated both as to type and concentration during the process of flotation A useful mode of characterization of lipoproteins is by use of the flotation rate in Svedberg units † (Sf units) under the arbitrary conditions chosen Obviously if a medium of density other than 1 063 gm/cc were used for the flotation process, the Sf rates would be altered, but should be perfectly reproducible in the new medium. The study of human serum low-density lipoproteins has revealed species with Sf rates from 2 to 40,000. The Sf 40,000 species is more familiarly known as the chylomicron Lindgren's work (4, 5) with these lipoproteins has demonstrated several discrete entities; the Sf2, Sf4, Sf6, Sf8, Sf10, Sf13, and Sf17 lipoproteins, differing from one another in chemical structure as well as in physical properties. Above Sf17, and

* The experimental work upon which this talk was based is that of a research group, including Hardin B. Jones, Frank Lindgren, Thomas Lyon, Beverly Strisower, Alex Nichols, Dean Graham, N K Freeman, and the author

† Svedberg unit = 10^{-13} cm/sec/dyne/gram.

DIET AND LIPOTROPIC AGENTS IN ATHEROSCLEROSIS *

John W. Gofman †

A RATIONAL APPROACH to the management of atherosclerosis and its clinical sequelae can best be made by a delineation of those aspects of the disease which may be accessible Two major features are striking about atheroma formation: 1) the definitely focal character of the lesions; and 2) the abnormality in serum lipids associated with the development of the disease.

Unfortunately our knowledge of the nature of the factors operative in producing the focal feature of atheroma formation is primitive. Until there is more light shed on this highly important problem, there is little hope of a therapeutic approach via the control of such factors. However, the discouraging state of our information concerning the basis for variable local vascular susceptibility to lesion formation should in no way be allowed to prevent a vigorous effort to cope with the general factors, namely, disturbed lipid metabolism and transport, which participate in the evolution of atherosclerosis. Whereas many investigators may disagree, the most plausible concept of the pathogenesis of this disease is that certain circulating lipids are deposited and retained in susceptible focal areas to produce atherosclerotic lesions. The various histopathologic features characterizing the lesions may then represent the result of secondary processes, including possibly regressive changes, in the evolution of the mature disease It is with the general factor, the lipid factor, that the present considerations are concerned

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lipoprotein components, even when all of them are present. This fact makes it difficult to predict the level of a particular lipoprotein, from a measurement of total lipoprotein level (or total cholesterol level). For example, one individual may characteristically show a ratio of Sf13/Sf17 twice as high as another, even though the total serum lipid levels are comparable From several lines of evidence our group has developed, it appears, both in the human and in several experimental animals (5), that the lipoproteins from Sf40,000 to Sf2 are metabolically interrelated. Chemical studies of the lipoproteins by Lindgren, Freeman, and Nichols (6) suggest the nature of this interrelation (see Figure 2). It is seen in

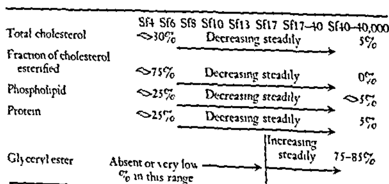


Figure 2 Chemical constituent.

Figure 2 that although cholesterol is a constituent of all the lipoproteins, it is a progressively more prominent constituent of the low molecular weight lipoproteins (those of low Sf value) *Neutral fat* is either absent or a very small fraction of the lipoproteins below Sf17 but becomes progressively more prominent in the higher Sf classes until it is the major chemical constituent in those above Sf 100. The present evidence suggests that fat (and possible certain other lipids, as *cholesterol*) of endogenous and exogenous origin may enter this system of lipoproteins in the form of high Sf lipoproteins (Sf30 to Sf40,000). As glyceryl ester is utilized off or transferred out of the blood, the higher Sf lipoproteins give rise to the successively lower members of the series. It is not possible at this time to determine whether a *given lipoprotein* of the high Sf classes necessarily goes through every one of the lower intermediate classes in

extending to Sf40,000, is a host of closely spaced components, or possibly a continuum of lipoproteins.

Human sera differ from one another in two respects: first, the number of types of lipoproteins present at appreciable concentration, and, second, the relative concentrations of the various species present. In spite of a wide variation extant among human patterns, the variations are by no means random. *It appears that only certain lipoprotein distribution patterns are allowed.* There is a regularity in the development of deviation from a particular pattern, which deviation may be a reflection of a progressive degree of metabolic error in the transport of serum lipids. This concept is illustrated in Figure 1. While there is a regular *progression of patterns from those showing only the Sf4 and/or Sf6* lipoproteins with inappreciable levels of any species of higher Sf values, and while the higher classes are never present unless all the lower classes are present at appreciable concentration, there is nevertheless only a partial relation between the serum concentrations of various individual

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"*Normal*" Pattern
(1) Lipoproteins of Sf4 and/or Sf6 present at low or moderate concentrations. *Minimal* levels of higher Sf components except for transient elevations in Sf30–40,000 following fatty meals.
"*Minimal*" Defect
(2) Lipoproteins of Sf4 and/or Sf6 at increased concentrations but without any increase in higher Sf components as compared with (1)
"*Minor*" Defect
(3) Lipoproteins of Sf4 and/or Sf6 *plus* Sf8 in increasing concentration.
Progressively "*More Severe*" Defect
(4) Sf4 + Sf6 + Sf8 + Sf10
(5) Sf4 + Sf6 + Sf8 + Sf10 + Sf13
(6) Sf4 + Sf6 + Sf8 + Sf10 + Sf13 + Sf17
(7) Sf4 + Sf6 + Sf8 + Sf10 + Sf13 + Sf17 + Sf17–20
(8) Sf4 + Sf6 + Sf8 + Sf10 + Sf13 + Sf17 + Sf17–20 + Sf20–40
(9) Sf4 + Sf6 + Sf8 + Sf10 + Sf13 + Sf17 + Sf17–20 + Sf20–40 + Sf40–40,000
(In this group the Sf40–40,000 can be of transient existence following meals or may be sustained even postabsorptively.)
(10) "*Most severe*" Defect
As in (9) except that the Sf4 and Sf6 may be depressed to quite low concentrations. (This may be regarded as a general *shift* toward higher Sf lipoproteins, and is comparable to that which appears in the rabbits in the later phases of cholesterol-Wesson oil feeding.)

Figure 1. *Lipoprotein transport as a measure of lipid metabolic defect (human).*

presumed normals of the same age and sex. The assumption, which is a reasonably safe one, is that on the average atheroma formation is proceeding in the coronary vascular bed at a greater rate in the frankly diseased group than in the normals. At best, we know from autopsy and other data that the "normals" are also atherosclerotic, although they are developing the disease with a rate of the order of one-half to two-thirds that of the "diseased" group. Further, the focal character of atherosclerosis will necessarily place certain individuals with minimal total atherosclerosis in the "diseased" category, when actually their rate of atherogenesis is less than that for many of the "normals." Other factors also operate to obscure our assessment The categorization of an individual as a "coronary" is a reflection not only of present rate of atherogenesis but also of *accumulated* atherosclerosis with its associated arterial narrowing In addition, there is the possibility that at a given time an individual may be developing atherosclerosis at a different rate from that which prevailed at other periods.

The above-described obstacles in reaching the goal, measurement of association of lipoproteins with atherogenesis, are indeed formidable, but not insuperable Their existence, however, makes it important to realize that whatever quantitative correlation is found between certain lipoproteins and atherogenesis is a *minimum* one. The true correlation must undoubtedly be much better than that which we measure, since all the obscuring factors have the effect of reducing the measurable relation

Quantitative Measurement of the Relationship of Lipoproteins with Atherosclerosis

In the experimental rabbit we have been able to produce a "spectrum" of lipoproteins generally similar in properties to that in the human It has also been possible to show in the rabbit that the rate of accumulation of atheroma is almost perfectly associated with the serum level of certain special classes of lipoproteins, but that it is not associated (or even inversely associated) with the serum levels of certain other classes

In making the assessment of the lipoprotein-atherosclerosis relationship in the human it is convenient to compare it with the observed relationship of serum cholesterol Small segments of the lipoprotein "spectrum" can be tested for association with atherosclerosis at the same time

the course of metabolism, or what the factors are which determine exactly where in the higher Sf classes lipid enters the system.

We may inquire now into the significance, metabolically, of elevated levels of the intermediate classes of lipoproteins. If, as the evidence indicates, the lipoproteins are related as an interconversion sequence, elevated levels of the intermediate members may be the result of excessive loading at the input end (the very high Sf classes), or a metabolic block in the rate of transformation from one class to another. In either event the result predicted would be an elevated steady state level of some or all of the intermediate lipoprotein classes. The degree of such a block and its particular position in the transformation sequence would largely determine which lipoprotein classes might be elevated. *One major effort in our study of the lipoprotein system is now directed* toward an understanding of the nature of the transformation blocking which appears to characterize so large a fraction of the adult human population.

Whatever factor is of major importance in a given case (i.e., excessive loading or transformation block), the human population presents itself with an array of serum patterns differing from one another in the *numbers of species of lipoproteins elevated in concentration* and in the degree of elevation. The immediate point of interest is the relationship of the serum concentration of individual classes of lipoproteins with the inception and progression of atheromatous vascular disease. It is evident that unless a positive relationship of this sort is demonstrable, considerations of management of atherosclerosis via lipoprotein level control would be meaningless. Ideally the quantitative assessment of the degree of association, if any, of each lipoprotein species with atherogenesis is the goal. Practical considerations of two types limit this, in part, in the human. First, it is readily possible to measure a band of lipoproteins, e.g., the total lipoprotein concentration between the limits of Sf10 and Sf20, whereas measurement of the concentration of a single species, e.g., Sf13 or Sf17, may be difficult. Secondly, assessment of the rate of atheroma formation in the living human is beset with difficulties. No direct measurement of this rate is available. A somewhat crude first approximation to this can be made by choosing a clinical entity largely superimposed upon an atherosclerotic background, such as clinically manifest coronary artery disease and comparing this with a group of

presumed normals of the same age and sex The assumption, which is a reasonably safe one, is that on the average atheroma formation is proceeding in the coronary vascular bed at a greater rate in the frankly diseased group than in the normals. At best, we know from autopsy and other data that the "normals" are also atherosclerotic, although they are developing the disease with a rate of the order of one-half to two-thirds that of the "diseased" group. Further, the focal character of atherosclerosis will necessarily place certain individuals with minimal total atherosclerosis in the "diseased" category, when actually their rate of atherogenesis is less than that for many of the "normals." Other factors also operate to obscure our assessment. The categorization of an individual as a "coronary" is a reflection not only of present rate of atherogenesis but also of *accumulated* atherosclerosis with its associated arterial narrowing. In addition, there is the possibility that at a given time an individual may be developing atherosclerosis at a different rate from that which prevailed at other periods.

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In making the assessment of the lipoprotein-atherosclerosis relationship in the human it is convenient to compare it with the observed relationship of serum cholesterol Small segments of the lipoprotein "spectrum" can be tested for association with atherosclerosis at the same time

the serum cholesterol is tested and the relative relationships determined In such testing procedures it has been possible to show that two particular segments are of especial interest, namely, the band of lipoproteins from Sf12 to Sf20 and the band from Sf20 to Sf100 (7, 8). A useful means of expressing the findings is at hand in the form of the "regression lines" between serum cholesterol and the particular lipoprotein class being considered. In essence such lines are simply a plot of the average lipoprotein level at each serum cholesterol, or conversely the average serum cholesterol level at each lipoprotein level. Figures 3A, B, and C present the critical data for 41–50 yr male "normals" and coronary patients for

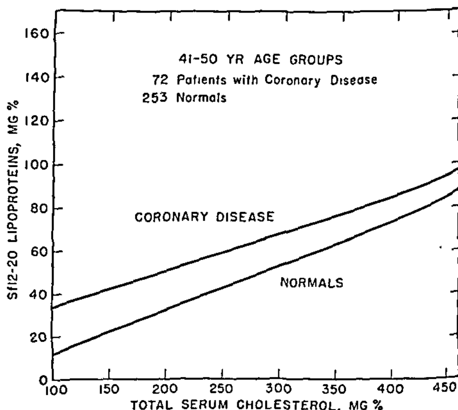


Figure 3A. The lines shown represent the average values of the Sf12–20 lipoprotein levels for any given cholesterol level It is seen that patients with coronary disease show higher Sf12–20 lipoprotein levels than do normals having the same serum cholesterol, throughout the range of serum cholesterols. Thus, the Sf12–20 lipoproteins have the ability to segregate coronary patients from normals *independent* of the serum cholesterol.

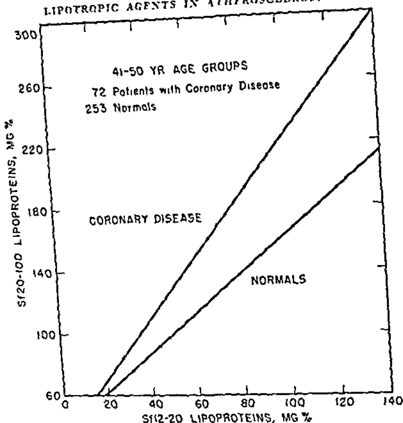


Figure 3B The lines shown represent the average values of the Sf20–100 lipoprotein levels for any given Sf12–20 lipoprotein level It is seen that patients with coronary disease show higher levels of Sf20–100 lipoproteins than do normals having the same Sf12–20 level. Thus, it is evident that the Sf20–100 lipoproteins segregate patients with coronary disease from normals independent of the segregation achieved by the Sf12–20 lipoproteins Both classes of lipoproteins, the Sf12-20 and Sf20–100, are of importance for atherosclerosis Both groups are associated with atherosclerosis, independent of the serum cholesterol level

serum cholesterol, the Sf12–20 lipoproteins, the Sf20–100 lipoproteins, and the combined Sf12–100 lipoproteins. Consideration of these figures leads to several important conclusions.

1 The band of lipoproteins from Sf12 to Sf20 (the "Sf12–20 class") is higher in the coronary group than in the normal group even when both

groups are compared at identical serum cholesterol levels, over the entire serum cholesterol range.

2. The band of lipoproteins from Sf20–100 (the "Sf20–100 class") is similarly higher in the coronary group than in the normal group even though the serum cholesterol levels are identical.

3. When the coronary group and normal group are compared at the same combined Sf12–100 level (i.e., Sf12–20 + Sf20–100) (see Figure 3C) the serum cholesterol level separates the two groups *much less* effectively than does the Sf12–100 level when the groups are compared at the same serum cholesterol levels. This finding implies that the remaining lipoproteins are of a lesser degree of atherogenicity than those of the Sf12–100 group.* It implies further that the important lipoproteins of the Sf12–100 class are marked by the much larger bulk of lipoproteins (approximately 85 per cent of the total lipoproteins) that are being assessed primarily when a serum cholesterol measurement is made. On the other hand the general trend toward rising Sf12–100 lipoprotein level with rising serum cholesterol levels means that as a crude first approximation the serum cholesterol level will show some correlation with atherosclerosis, although this correlation is less than that for the Sf12–100 lipoproteins with atherosclerosis. Further, since the Sf12–100 level can be high when the total cholesterol is low, or low when the total cholesterol is high, individual cases may be seriously misclassified as to atherogenic potentialities by a simple serum cholesterol measurement.

The question may now again be raised as to the actual strength of the relationship between the Sf12–100 lipoproteins and atheroma development From the earlier consideration of obscuring factors we can be assured that the true strength of the relationship is much greater than that which we have been able to demonstrate. Reasonable estimates of how much obscuring factors might reduce the observed relationship together with estimates of errors in measurements (5) have led us to the conclusion that the Sf12–100 lipoproteins account for the great bulk of the general metabolic factors which lead to atherosclerosis

* Present evidence indicates that much of the residual association with atherosclerosis is due to the Sf 8–12 lipoproteins. Possibly some may be due to lipoproteins above Sf 100. This would still leave the major bulk of the serum cholesterol in the form of nonatherogenic or, at best, weakly atherogenic lipoproteins.

(72 Patients with Coronary Disease) Mean Serum Cholesterol	= 304 mg % (Standard Error = 4 mg %)
253 Normals Mean Serum Cholesterol	= 260 mg % (Standard Error = 6 mg %)
Difference in Serum Cholesterol	= 44 mg % (Standard Error = 7 mg %)

Lipoprotein Class	*Difference between coronary patients and normals in mg % lipoprotein*	*% Cholesterol † in lipoprotein class*	*Difference between coronary patients and normals in mg % cholesterol*
Sf10-12 *	8 2 mg %	30%	2 5
Sf12-20	23 9 mg %	25%	6 0
Sf20-100	72 mg %	20%	14.4
Sf100 *	20 mg % (minimum estimate)	~6%	1.2
			Sum = 24 1 mg %

From the independent measurement of the intercorrelation of the Sf12-20 lipoproteins with the Sf0-8 lipoproteins, the coronary group should be 32 mg % higher in Sf0-8, on the basis of this intercorrelation alone Sf0-8 lipoproteins contain 35% cholesterol Thus (32) (0 35) = 11.2 mg% cholesterol is *expected* difference between coronary and normal population This may be added to the 24 1 mg% already accounted for since it represents no *independent* contribution of the Sf0-8 lipoproteins.

Thus 24 1 + 11 2 = 35 3 mg% cholesterol difference is accounted for in Sf10-100 + class of lipoproteins

Remainder 44 − 35 3 = 8 7 mg% cholesterol.

This small remainder, which cannot be proven *significant* from these data, is all that remains for possible independent contribution from the remaining bulk (~85%) of the serum cholesterol to atherosclerosis It is evident, therefore, that this bulk of serum cholesterol *shows very little*, if any, independent association with atherosclerosis

* Sf10-12 lipoprotein levels correlate very highly (r = 0.8) with Sf12-20 lipoprotein levels
Sf100+ lipoproteins correlate highly with Sf20-100 lipoproteins
† See reference 6.

Figure 3C Comparison of the Sf12-100 lipoprotein-atherosclerosis relationship with that of the remaining bulk of serum cholesterol

There is, then, a class of lipoproteins in human serum highly associated with atheroma development It cannot be proven at this time that this association is an etiologic one. However, our concept of atherosclerogenesis is that the lipids of lesions originate from the blood, and it is hence highly likely that the Sf12-100 lipoproteins represent the actual blood source of those lipids Unless the developing evidence

should contradict this view, it may be considered feasible to attempt the management of atherosclerosis through measures directed toward the reduction of the serum level of the Sf12–100 lipoproteins. It is worth pointing out here that the objective is not necessarily reduction of total serum cholesterol levels.

Thus if a shift from the atherogenic Sf12–100 lipoprotein classes to other less atherogenic or nonatherogenic lipoproteins could be produced without any drop in total serum cholesterol level the desired objective might be attained. Conversely if a drop in serum cholesterol is achieved with a concomitant shift into the Sf12–100 class, the effect would very likely be an increase in atheroma formation rather than a decrease.

Dietary Approaches to Atherosclerosis

a) Caloric intake and obesity. It is a matter of fairly general agreement that obesity is almost wholly the result of the ingestion of an excess of calories in the diet. Clinical and insurance experience (9) have shown that a positive relationship exists between obesity and atherosclerotic vascular disease. No satisfactory explanation of this relationship had been adduced from the semipopular view of an excessive "work burden" for the heart. Our own evidence suggests a very different basis for this relationship of vascular disease to obesity. Since the Sf12–100 lipoproteins are associated with atherosclerosis, we have endeavored to assess the extent to which obesity contributes to elevation in the serum Sf12–100 lipoprotein level Ideally a direct estimate of the body fat content of the studied subjects should be made. Since such measurements were not available during the study, a crude measure of obesity was obtained from height-and-weight measurements and a table of ideal height-weight relationships (10) In a group of 253 male subjects a definite positive correlation was found between estimated obesity and Sf12–100 lipoprotein level (crude correlation coefficient = 0.3). If account is taken of two factors, the crudity of height-weight measures as an estimate of obesity and the biologic and technical variation in Sf12–100 lipoprotein measurements, it becomes certain that the true relationship of Sf12–100 lipoproteins with obesity must be considerably higher than the measured one. A reasonable estimate of such factors indicates that the order of 20 per cent of the factors contributing to elevation of the

Sf12–100 lipoprotein levels are directly related to obesity. This means that obesity may account for approximately 20 per cent of atherosclerogenesis via the Sf12–100 lipoproteins.

The practical, clinical implications of this relationship deserve to be stressed The "normals" who escape manifest coronary artery disease have atherosclerosis, but of lesser quantitative degree than do patients with frank coronary disease (perhaps of the order of 30 per cent less). Therefore reductions in rate of development of coronary atherosclerosis of 10–20 per cent might be anticipated to provide a very significant decrease in the occurrence of clinical sequelae of coronary sclerosis It can be predicted that reduction of caloric intake and, hence, correction of obesity may certainly be expected to do at least this much on the basis of the Sf12–100 lipoprotein relationship with overweight. Our experience with patients has amply indicated reduction in Sf12–100 levels as caloric intake is dropped and obesity is lessened There is considerable individual variation in the extent of Sf12–100 lipoprotein reduction which results from caloric restriction and weight loss. This individual variation is, however, to be expected since the correlation of Sf12–100 level with overweight is quite definite but not high enough to assure uniformity of response. In certain individuals the drop in Sf12–100 level associated with weight loss is quite marked and may well ultimately prove to be a major factor in prevention of premature coronary disease. It has been suggested that the mobilization of endogenous fat during a period of weight loss might result in elevation of the serum levels of certain lipoproteins and that this might be deleterious. At present our experience indicates that the Sf12–100 lipoprotein levels fall during the actual period of weight loss However, it is conceivable that further study of this problem may show that in certain individuals a rise in level may occur during weight loss

b) Dietary fat intake Since at least part of the fat in the various lipoprotein classes is of exogenous origin (11), it is of importance to know to what extent dietary loading with fat results in elevation of the Sf12–100 levels The investigation of lowering fat intake clinically is hampered by the fact that the patients studied generally tend to lose weight, at least in the initial periods of fat restriction This weight is not usually regained in the patients who continue to adhere to the low fat diet. Thus even though such patients show, in a high proportion of cases, a signifi-

cant lowering in Sf12–100 levels, it is difficult to segregate out that part of the effect due to lowering of caloric intake and weight from that due to lowered dietary fat loading.

However in other patients studied the serum Sf12–100 lipoprotein level drops even when there is no appreciable weight alteration on a diet restricted in total fat intake. These studies indicate an effect of the dietary fat separate from the calorie-weight effect. The human population appears quite inhomogeneous in this response to fat restriction At present it is not possible to predict which patients will respond to dietary fat restriction from the lipoprotein pattern or from any other consideration. Excluding cases where the diet has not been adhered to, there are still unquestionably cases where fat restriction does not reduce Sf12–100 levels. The initial lipoprotein pattern in such individuals does not appear significantly different from that in cases where restriction in fat does produce drops in Sf12–100 levels At present the individual's response to a lowering fat intake is determined by actual trial, with serial lipoprotein studies

Thus dietary measures, including caloric restriction and fat restriction, are capable of reducing elevated Sf12–100 lipoprotein levels in a part of the human population. Neither measure is universally effective in reducing lipoprotein levels. However, the response to one or another of the measures is of sufficient degree and frequency to warrant the trial of a low fat diet plus obesity correction as an approach to Sf12–100 lipoprotein reduction in the management of atherosclerosis.

"Lipotropic" Agents

The desirability of a pharmacologic approach to the lowering of the Sf12–100 lipoprotein level is self-evident, if we accept the hypothesis that these serum lipoproteins represent the source of atheroma lipids. There might well be objection to the use of the term "lipotropic agent" to describe a substance capable of reducing the Sf12–100 level. Possibly the only justification for the use of this term with respect to the present problem is the fact of its widespread use in this connotation.

The one pharmacologic agent showing a marked effect upon the Sf12–100 levels and upon serum lipoprotein distribution in general is heparin. A detailed publication of the findings of Graham et al. of our laboratory has appeared (12). The effect of heparin upon the serum lipo-

proteins in the human is of especial interest since it appears to be such as to shift lipoprotein patterns in the direction of normality. Subsequent to the injection of a single dose of 25–100 mg of heparin intravenously, there is a progressive reduction in levels of the lipoproteins of very high Sf classes (above Sf20) with transitory increases in the intermediate classes (Sf10–20 class). Subsequently the Sf10–20 lipoprotein level may decrease with a concomitant rise in the level of lipoproteins below Sf10. The reduction in level of lipoproteins above Sf20 (Sf20–100 and higher classes) is striking within 5 to 20 minutes following intravenous heparin injection. The progressive transformations continue over a period of several hours. Within 24 hours after a single heparin dose in the range of 25–100 mg most humans show a reversion to the pre-heparin lipoprotein pattern. Most striking of all the changes is the ability of heparin to produce *essentially* a "wipe-out" of the serum lipoproteins above Sf20. Since a major constituent of the lipoproteins above 20 Sf units is glyceryl ester (neutral fat), this represents a removal from the entire blood *volume* of quantities of the order of several grams of fat. The fate of the fat thus cleared from the blood is now under investigation. In general it appears that the dose of heparin required to wipe out the Sf20–100 lipoproteins is greater the higher the level of such lipoproteins originally.

Since the shift in lipoproteins under the influence of heparin is in the direction that normal interconversion pathways appear *to follow*, it *seems* possible that heparin in a combined form, or some *related* system, is normally *involved in* lipoprotein interconversion in the human. Abnormal serum lipoprotein distributions *might then* be the result of a quantitative inadequacy of heparin in the appropriate form for handling the lipid load. This question is now under active investigation.

The serum lipoprotein shift produced by heparin appears favorable with respect to the atherosclerosis problem since the level of the atherosclerosis-associated Sf12–100 lipoproteins is markedly reduced. Graham et al. (12) have shown that heparin suppresses the rise of Sf10–50 lipoprotein levels and suppresses atherosclerosis in the cholesterol-fed rabbit. The possibilities of similar application of heparin in human atherosclerosis would be facilitated by the availability of an acceptable long-acting heparin, so that the Sf12–100 lipoproteins might be chronically suppressed. The effects of long-term use of heparin for the purpose of lipoprotein alteration will become clarified as a result of further studies.

In any event this agent has produced striking alterations in lipoprotein distributions which assure the possibility, at least, of lipoprotein control through pharmacologic means. If it also sheds light upon the naturally occurring factors which account for normality or deviation therefrom in lipoprotein transport, atherosclerosis research will have been materially advanced

Summary

1. The ultracentrifugal study of human serum allows the characterization of lipid transport in terms of a "spectrum" of lipoproteins.

2. The type of lipoprotein transport characteristic of an individual is apparently a reflection of the degree of deviation from normal lipid metabolism.

3. Certain of the lipoprotein classes, the Sf12–20 and Sf20–100 classes, show a high quantitative association with atherosclerogenesis in the human. This association is manifest independent of total serum cholesterol level.

4. Obesity is associated with elevation of the Sf12–100 lipoproteins This association may be adequate to account for the excessive atherosclerosis in the obese

5. Reduction in caloric intake and weight lowers Sf12–100 levels to variable degrees in the human population Reduction of dietary fat has a similar effect in part of this population.

6. Heparin administration to humans produces a shift in lipoprotein patterns toward normal.

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CORONARY DISEASE: CLINICAL-PATHOLOGIC CORRELATIONS AND PHYSIOLOGY *

Herrman L. Blumgart †

THE CIRCULATION *of the heart presents many interesting differences from the rest of the body. Skeletal muscle on vigorous contraction can increase its oxygen consumption thirtyfold or more.* This vastly increased requirement is met in part by an increase in arterial and capillary blood flow and in part by extracting more oxygen from each unit of blood passing through the capillaries. Thus, the oxygen content of venous blood, which is approximately 12 volumes per hundred cubic centimeters with skeletal muscle at rest, may be reduced to 5 volumes per cent or less on exercise This ability to borrow on the "reserve" oxygen is not enjoyed by the heart. The venous blood of the coronary sinus under normal conditions contains only 2 to 5 volumes per cent of oxygen. There is little to borrow and so the heart must "pay as it goes" by increasing the coronary arterial blood flow proportionately when the myocardium needs more oxygen to do more work. *Skeletal muscle is also different in that it can continue to contract during exercise, even if the oxygen supply is momentarily inadequate, by incurring an oxygen debt which is repaid later during rest.* The myocardium, however, does not possess this ability, it depends for its contractility on the oxygen immediately available from coronary blood flow.

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† From the Medical Research Department of the Yamins Research Laboratories of the Beth Israel Hospital, Boston, Mass., and the Department of Medicine, Harvard University Medical School, Boston, Mass
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It ceases to contract when it has incurred only one fifth of the oxygen debt skeletal muscle can endure.

Skeletal and cardiac muscle also present an interesting difference in their vascular supply. The smaller arteries and arterioles of striated muscle freely communicate with each other by large anastomotic vessels. Except for sudden occlusion of large trunks such as the brachial, iliac, or femoral arteries, infarction of muscle is rare. The coronary arteries, on the other hand, are, in a physiological sense, end arteries. In 1669, Richard Lower stated that ". . . the vessels which carry blood to the heart . . . come together again, and here and there communicate by anastomoses." It has gradually become the consensus, however, that the connections that exist *normally* between the coronary arteries are only fine communications of an arteriolar or capillary nature which are less than 40 microns in diameter. These intercommunications, while of some limited functional value, are not sufficient to prevent infarction of the myocardium when coronary arteries are ligated experimentally in animals or are suddenly occluded by thrombi or emboli in man. In a functional sense, therefore, the coronary arteries are end arteries (1, 2, 3).

Obviously, therefore, anatomical patency of the coronary arteries is of cardinal importance in the maintenance of normal cardiac nutrition and performance. The very large extraction of available oxygen by the normal heart, the inability of the myocardium to incur a sizable oxygen debt, and the fact that coronary arteries are functional end arteries in the normal heart make it mandatory that any significant increased oxygen need by the heart must be met by an increase in coronary blood flow. Failure to meet the demands of the myocardium as a whole may lead to congestive heart failure, ischemia of certain areas may lead to the clinical symptom of cardiac pain, disturbances of impulse formation, and the occurrence of arrhythmias, if the ischemia is sustained, actual injury or necrosis of heart muscle may develop.

It is of paramount importance to recognize that the adequacy of coronary blood flow is always to be considered in relation to the requirements of the myocardium to accomplish its work. The coronary blood flow may be adequate to meet the normal myocardial needs at rest, but insufficient for the increased requirements when the work of the heart is increased as in exercise, emotion, thyrotoxicosis, fever, or rises in

blood pressure. In such circumstances myocardial ischemia develops with its clinical representation of cardiac pain or discomfort. That this imbalance between supply and demand underlies cardiac pain is supported by an impressive body of evidence.

Many diseases may affect the coronary arteries and encroach on their lumens. Thromboembolic obstruction of a coronary artery, syphilitic aortitis with narrowing of the coronary ostia, periarteritis nodosa, thromboangiitis obliterans, rheumatic arteritis, scleroderma, amyloidosis, and the arteritis associated with systemic infection may be encountered. These conditions are responsible for less than 10 per cent of all coronary artery disease. Atheromatosis leading to arteriosclerosis with narrowing and complete obstruction is the most prevalent lesion responsible for more than 90 per cent of coronary artery disease.

To gain further insight into the meaning of the clinical signs and symptoms of heart disease, a detailed study has been made during the past ten years of the clinical cardiac manifestations together with an *injection plus dissection of the heart in every necropsied case* at the Beth Israel Hospital in Boston The series now comprises over 1600 hearts examined by the method developed by our pathologist, Monroe J. Schlesinger (4) The right, the left anterior descending, and the left circumflex coronary arteries were injected simultaneously with differently colored radiopaque masses under a pressure of from 150 to 200 mm of mercury The heart was unrolled so that all of the coronary arteries lay in one plane, and a roentgenogram was made A complete dissection of the arteries was then carried out with the roentgenogram as a guide.

The degree of narrowing of the coronary arteries was classified in each heart as slight, moderate, or marked Arteriosclerotic changes without any discernible narrowing of the lumen, such as small intimal atheromata, were not regarded as functionally significant and were placed in the normal group without narrowing "Slight narrowing" refers to hearts with slight but definite constriction of the lumen, "marked narrowing" signifies unequivocal, extreme reduction in the lumen at one or more points in the coronary arterial tree, "moderate narrowing" includes all hearts with intermediate degrees of narrowing In a small group of hearts the internal diameters of the major vessels were measured by a series of graduated probes, so that the percentage reduction

in diameter at areas of narrowing in comparison with immediately adjacent zones was quantitatively determined. Slight narrowing was found by quantitative estimate to correspond approximately with a reduction in diameter of 25 per cent or less, marked narrowing was equivalent to 75 per cent reduction or more.

Observations in the Normal Heart

The significance of structural abnormalities in patients with angina pectoris or acute myocardial infarction can be appraised only in the light of the findings in patients without angina pectoris or acute myocardial infarction We examined the hearts of over 200 persons who died of noncardiac causes in whom we found no coronary arteriosclerosis and who had had no clinical evidence of arteriosclerotic disease.

In these normal hearts, as previously stated, fine connections of an arteriolar or capillary nature are observed between the coronary arteries. They are less than 40 microns in diameter. These anastomoses are readily disclosed by the simple observation that when a colored watery solution which reaches the capillary bed is injected into one coronary artery, it promptly appears in the other coronary arteries and their ramifications When, however, colored radiopaque lead phosphate agar masses are injected into the three main coronary arteries, according to the technique of Schlesinger, there is no intermixture of color. Since the lead-agar suspension penetrates regularly only as far as arterioles 10 to 40 microns or more in diameter, the larger interarterial collateral pathways of 40 microns or more may be regarded as generally absent in normal hearts Patients even seventy or more years of age who have normal coronary arteries show no intercoronary anastomotic vessels (Figure 4) The development of an anastomotic circulation is not a necessary concomitant of the aging process.

Observations in Cases without Clinical Cardiovascular Disease in Which Coronary Narrowing or Occlusion Was Present

In approximately 40 per cent of all patients above forty years of age who died of noncardiac causes such as carcinoma, and who had no cardiac pain, congestive failure, or other manifestation of heart disease, complete occlusion or considerable narrowing of one or more coronary

arteries was seen (Figure 5). Despite these obstructive lesions, the myocardium was usually normal on gross and microscopic examinations. In many instances, electrocardiographic tracings were normal. This apparent inconsistency between the presence of long-standing, obstructive lesions, on the one hand, and the absence of pathologic or clinical evidence of myocardial damage, on the other, was dispelled by the demonstration

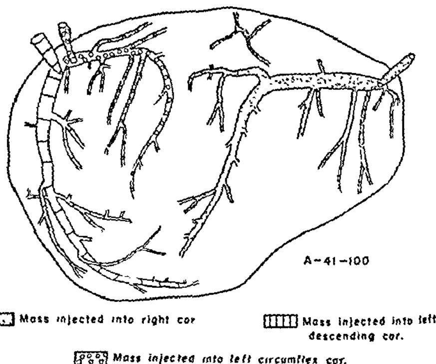


Figure 4 (Case A-37-78). Diagram of normal coronary arterial tree of a man aged 72, who died of fibrosarcoma of the femur The heart was normal, and there was no arteriosclerosis or other abnormality in the coronary arteries

with the Schlesinger injection mass of the larger than normal collateral channels (Figure 6) These collateral vessels by-pass the obstructions, or supply the myocardium distal to the areas of narrowing or occlusion from neighboring unoccluded coronary arteries The anastomotic circulation evidently develops as a compensatory phenomenon in relation to gradually occurring arterial occlusions Although serious damage may be avoided by the development of such collateral circulation, the margin of safety, or, as it may be termed, "the coronary reserve" is presumably reduced.

The collateral pathways of the "Thebesian" type, which hitherto have attracted particular attention, communicate between the cavities of the heart and the arteries of the heart, or between the cavities of the heart and the capillaries or veins. The collateral pathways demonstrated in abnormal hearts by the lead-agar mass communicate between coronary arteries and, therefore, would appear to be more significant in the maintenance of capillary blood flow. While the collateral circulation tends to protect the heart from serious myocardial damage, the occurrence of a sudden occlusion may result in acute myocardial infarction, particularly if time has been insufficient for the development of adequate anastomotic vessels or if the demand for blood by the myocardium at the time is excessive

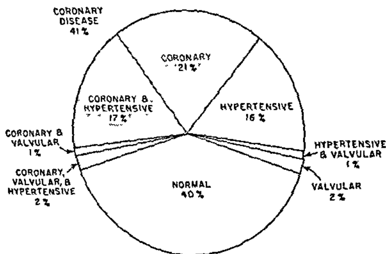


Figure 5 Incidence of cardiac pathology in the absence of cardiac symptoms in 532 cases without cardiac hypertrophy

The general older view of coronary arteriosclerotic heart disease as a simple progressive narrowing with final closure due to thrombosis is, therefore, no longer tenable. One must, instead, consider that the final effect on the myocardium is the resultant of two opposing factors 1) the reduction of blood flow due to narrowing and complete occlusion and 2) the compensatory development of larger than normal collateral channels which offset the dire consequences of narrowing or occlusions.

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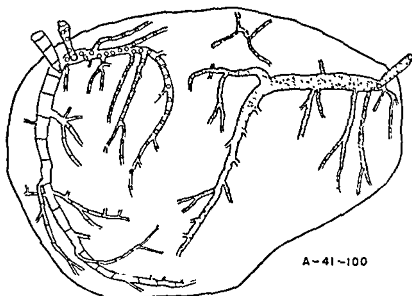


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croscopically showed, in addition, that these collateral channels not only permitted survival of the animal but at times safeguarded the myocardium from serious damage. In some hearts, indeed, not even scattered microscopic necrosis was found. In brief, these experiments demonstrate that the large collateral channels may be produced in response to marked coronary narrowing, that 5–12 days are needed for their ample development, that they enable survival following subsequent complete acute occlusion and protect the heart from serious damage.

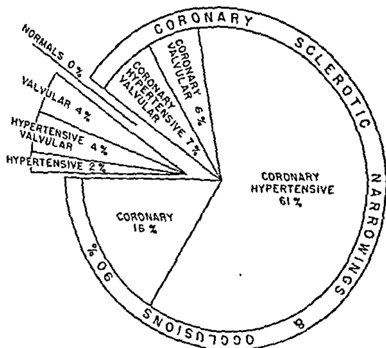


Figure 7 The etiologic substrate of angina pectoris based on 177 cases

Observations in Patients with Angina Pectoris

In contrast to the observations so far described, the hearts of patients who had suffered attacks of angina pectoris showed a striking increased prevalence of severe arteriosclerotic coronary narrowings and occlusions (6). Ninety per cent of the hearts of patients with angina pectoris showed such obstructive narrowings and occlusions; in the majority, at

It is obviously of considerable theoretical and practical importance to know the conditions which favor the development of the larger anastomotic channels and the length of time necessary for their establishment. Clinical and pathological experience offers no answers to these questions. Therefore, recourse to animal experimentation was necessary (5). The heart of the pig was chosen for the studies since it most nearly

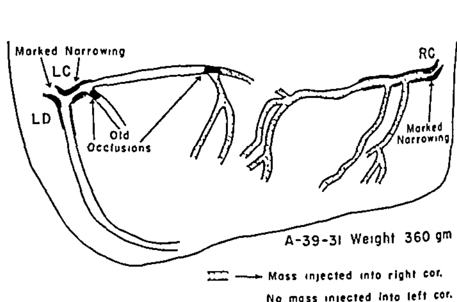


Figure 6. (Case A-39-31). Diagram of coronary arterial tree. Unilateral injection of lead-agar mass into right coronary artery No angina pectoris or congestive failure. Death due to biliary obstruction

Necropsy Carcinoma of pancreas and stone in ampulla of Vater. Complete occlusions of main stem and primary branch of left circumflex artery Vessels distal to occlusions injected by collateral circulation from right coronary artery. Myocardium showed moderate fibrosis and no infarction

resembles that of man. In some forty consecutive experiments ligation of the left anterior descending artery or the right coronary artery invariably resulted in death. When 75 per cent narrowing of either of these arteries was produced for twelve or more days, studies of the heart, post mortem, showed a rich anastomotic circulation had developed which served as a detour around the arterial narrowing in each of the hearts. It was found, furthermore, that after 5 to 12 days, sudden acute occlusion of the narrowed artery could be done and that the animal now would survive. Examination of the myocardium grossly and mi-

ing congestive failure, rapid auricular fibrillation, increasing engorgement of the liver, and he died on the seventh hospital day.

Pathology The heart weighed 615 gm There was considerable diffuse fibrous myocarditis throughout the heart, but no old or fresh infarcts. The valves were normal

Coronary arteries There was advanced arteriosclerotic involvement of the entire coronary tree Multiple points of extreme narrowing and nine complete old occlusions involving all three coronary arteries and several branches were observed In addition, a recent organizing thrombus was found in the left anterior descending coronary artery, just distal to a point of old occlusion An extremely well-developed anastomotic circulation was present with a very rich network of fine, injected vessels throughout the heart Many grossly dissectible connecting channels could be traced from one coronary artery to another. Extensive myocardial fibrosis was found throughout the left ventricle

Comment This case with multiple narrowings and occlusions involving all three major coronary arteries demonstrates the remarkable compensatory capacity of the anastomotic circulation of the heart Collateral circulation had developed in sufficient degree to prevent myocardial infarction in spite of this extensive coronary arterial obstruction Myocardial weakness resulting in congestive failure in the last few weeks of life was apparently caused by extensive replacement of muscle with fibrous tissue The terminal severe infection, high fever, and renal insufficiency imposed a greater load upon the coronary circulation than it could sustain The more rapidly progressive myocardial damage with congestive failure and terminal scattered myocardial necrosis are expressions of the final failure of the coronary reserve The fresh, occluding thrombus in the left anterior descending coronary artery was between two old complete occlusions and could cause no further impairment of coronary circulation It probably resulted from the slowed, sluggish, coronary blood flow in this segment of the coronary tree

In the other 10 per cent of the cases, arterial hypertension with cardiac hypertrophy or valvular lesions was responsible for the clinical manifestations The chief effect of these lesions was to interfere with coronary blood flow or increase the requirements of the myocardium for blood, thereby leading to relative inadequacy of blood supply to the myocardium Arterial hypertension and valvular disease greatly increase cardiac work even under basal conditions and, therefore, limit the degree to which the work of the heart may be augmented, as on effort, without inducing relative ischemia and cardiac pain

Our clinical and pathologic studies show that coronary arteriosclerosis, arterial hypertension, and valvular heart disease, alone or in combination, form the etiological substrate of all cases of angina pectoris. In

least one main coronary artery or one of its primary branches was occluded (Figure 7). The severity of coronary arteriosclerotic involvement in angina pectoris is illustrated by the following case (Figure 8).

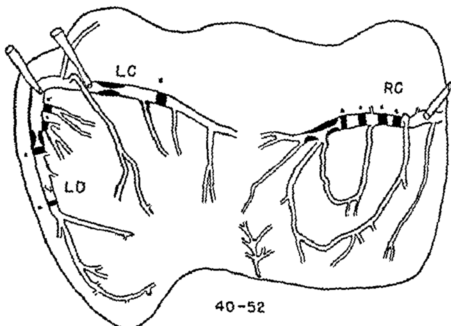


Figure 8 (Case 40-52) Diagram of injected heart Nine old complete occlusions in three major coronary arteries and primary branches. Several areas of narrowing One fresh occlusion between old occlusions in left anterior descending artery

CASE 40-52, B D, MALE, 68 YEARS

Angina pectoris, sixteen months, congestive failure, five weeks, hemiplegia, sixteen months, no symptoms of myocardial infarction Death due to urinary tract infection of five days' duration with pneumonia and congestive failure

Nine complete old occlusions in the three main coronary arteries and branches; one fresh occlusion and several areas of marked narrowing, no myocardial infarction but marked diffuse fibrosis, rich anastomotic circulation

Patient B D (40-52), a 68-year-old man, had had frequent severe attacks of angina pectoris for 16 months relieved by nitroglycerin Five weeks before admission he developed signs of congestive failure which was favorably affected by treatment. He had suffered a left hemiplegia 16 months before admission He entered the hospital seven days before death because of a severe urinary tract infection accompanied by chills, high fever, dysuria, and pyuria with a white blood cell count of 24,000 Despite chemotherapy, the patient showed increas-

ng congestive failure, rapid auricular fibrillation, increasing engorgement of the liver, and he died on the seventh hospital day

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Our clinical and pathologic studies show that coronary arteriosclerosis, arterial hypertension, and valvular heart disease, alone or in combination, form the etiological substrate of all cases of angina pectoris. In

all 177 instances of angina pectoris in the series, evidence of such cardiovascular disease was found. Coronary arteriosclerotic disease was present in 159, or 90 per cent, of the group with angina. In those due to coronary arteriosclerosis, the majority (108 of the 159) showed old complete occlusions of one or more main coronary arteries or primary branches. In these 108 hearts, 312 old occlusions were found, or an average of 2.9 occlusions per heart. Marked and moderate coronary narrowing alone may at times produce angina pectoris, but slight coronary narrowing *per se* is apparently an inadequate stimulus for the production of this symptom.

To clarify the mechanism underlying episodes of angina pectoris in patients with coronary artery occlusions, myocardial fibrosis was studied in patients with and without angina pectoris. The prevalence of myocardial fibrosis and of intercoronary anastomoses in these hearts is consistent with the hypothesis that angina pectoris, myocardial fibrosis, and intercoronary anastomoses all result from myocardial ischemia; angina pectoris is a clinical expression, myocardial fibrosis a pathological end result, and intercoronary anastomoses a compensatory response to ischemia All hearts with old occlusions are found to have anastomoses by the Schlesinger technique. The absence of fibrosis in some hearts with old coronary occlusion is due to the adequacy of the compensatory collateral circulation which developed in response to the occlusions.

While there is a general relationship between the incidence of coronary occlusions and the occurrence of angina pectoris, other modifying factors such as the exact site of the occlusion, the importance of the vessel involved (7), the adequacy of the collateral circulation, the rate at which such occlusions or narrowings develop, the temporary influence of emotion and of vasomotor reflexes are also of great importance (8, 9). In patients, previously well, who suddenly suffer attacks of mild or severe angina pectoris on but little exertion, the occurrence of rapidly progressive narrowing or of sudden complete occlusion of a coronary artery must be considered if no other cause for reduced coronary blood flow or increased myocardial requirement is found on clinical evaluation. A similar explanation for reduced coronary reserve must be entertained in patients with long-standing angina pectoris if attacks are suddenly more readily precipitated. Under such circumstances bed rest is strongly

advisable to decrease the demand on the heart while the development of a more adequate collateral circulation may ensue.

"Spasm" of the coronary arteries with diminished blood flow has also been invoked frequently to explain the precipitation of episodes of angina pectoris Attacks of angina brought on by exposure to cold or "by a disturbance of mind" (10) and prevented or terminated by nitroglycerin are difficult to explain solely on the basis of long-standing anatomical changes in the coronary arteries or myocardium Spasm could result from a direct effect of epinephrine or other circulating substances on the smooth muscle of the arteries, or it could be induced by vasomotor reflex impulses. The vast accumulation of experimental observations of coronary vasoconstriction in animals cannot be transposed to man with assurance, but recent observations in patients with angina pectoris now afford strong evidence of the existence and significance of vasomotor influences. Vasomotor reflex changes account in part at least for the effects on anginal attacks of atropine, local chilling and anesthesia of the hands (11), carotid sinus stimulation, tobacco smoking, pulmonary emboli, and gastrointestinal disorders Indeed, reflex coronary vasomotor spasm may be important in increasing the extent of myocardial necrosis and the mortality following acute coronary artery occlusion (6, 12).

The existence of vasomotor effects which reduce coronary flow is in no way incompatible with the demonstration and importance of widespread pathologic changes in the hearts of patients with angina pectoris. The primary etiological factors of coronary obstruction, valvular disease, and arterial hypertension are not to be considered the exclusive cause of cardiac pain, rather they constitute the stage upon which various transitory factors may operate. Thus, coronary vasoconstriction, anemia, tachycardia, hypermetabolism, or hypotension may act as precipitating agents in the production of pain in a patient whose coronary circulation is already compromised by arterial obstruction In the absence of an adequate pathologic substrate, these factors rarely, if ever, are sufficient in themselves to produce angina pectoris.

The underlying mechanism, then, of angina pectoris appears to be a relative disproportion between the requirements of the heart for blood and the supply furnished by the coronary arteries This disproportion results in paroxysmal ischemia with its clinical counterpart, an attack of

angina pectoris. In accordance with this concept, angina pectoris is precipitated by states which increase the work of the heart such as effort, emotion, and is relieved by coronary vasodilators such as nitroglycerin or amyl nitrite or by decreasing the cardiac work by rest or medication. The extraordinary significance of the collateral circulation in bridging the discrepancy between supply and demand is of pathologic and clinical importance.

Acute Myocardial Infarction

The clinical diagnosis of acute myocardial infarction is based on prolonged pain indicative of prolonged ischemia plus the clinical expressions of myocardial necrosis. These consist of shock, characteristic progressive electrocardiographic changes, fever, leukocytosis, and increased sedimentation rate. The primary cause is an inadequate coronary blood supply. Occlusion by thrombosis, subintimal hemorrhage, rupture of an atheromatous abscess, or embolism is usually responsible. Temporary reduction in coronary blood flow or increased work of the heart, in the presence of a previously compromised circulation, may lead to infarction without the occurrence of fresh coronary arterial lesions. Since the myocardial infarct is the pathologic lesion responsible for the clinical syndrome, and since the presence, absence, or exact character of the arterial obstruction cannot be diagnosed clinically, it is more accurate to use the term "acute myocardial infarction" rather than designations such as coronary thrombosis, coronary occlusion, coronary insufficiency, and so on.

Atherosclerosis is the most frequent etiology, but in a very few cases, arteritis due to syphilis, rheumatic fever, systemic infections, or thromboangiitis obliterans may be responsible. Acute myocardial infarction may be the first clinical manifestation of coronary atherosclerosis when a single area of atheromatosis in an otherwise quite normal coronary arterial tree becomes the site of a fresh thrombus (Figure 9).

CASE 37-2, W G, MALE, 50 YEARS

Close supervision for nine years because of gastrointestinal complaints; paroxysmal auricular tachycardia, four years, no congestive failure; angina pectoris, eleven days; coronary thrombosis, myocardial infarction, and death.

Narrowing of left anterior descending and left circumflex arteries; freshly deposited thrombus completely occluding left circumflex artery, myocardial infarction and subsequent rupture of the heart

W. G., 50 years old, had been under close medical supervision for nine years because of ill-defined abdominal distress without obvious evidence of any abnormalities on physical examination or x-ray. Blood pressure had been normal. During four years before death he had had occasional episodes of paroxysmal auricular tachycardia but at no time showed any evidence of cardiac pain despite fairly heavy work and emotional tension. Beginning eleven days before death he suffered attacks of substernal pain induced by mild exertion, cold, and excite-

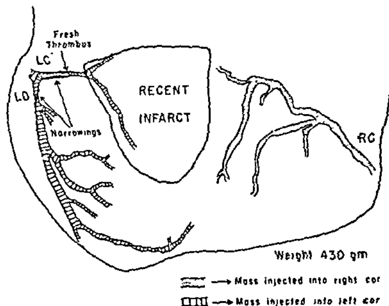


Figure 9 Diagram of injected heart of case 37-2

ment, relieved by nitroglycerin. He was admitted to the hospital six days before death because of persistent excruciating substernal pain. Physical examination was essentially negative except for persistent fever and characteristic progressive electrocardiographic evidence of acute myocardial infarction. Pain had subsided and he was feeling better when he suddenly became ashen, dyspneic, and died.

Post-mortem examination The heart weighed 430 gm. There was a large fresh infarct of the posterior left ventricle near the base with a tear of the myocardium 1 cm long at the anterior border of the infarct. The right coronary artery was normal. The left anterior descending coronary artery was narrowed near its origin. The left circumflex artery showed an area of atheromatosis with considerable narrowing near the origin with a large occluding thrombus. The portion of the heart distal to the occlusion was only poorly filled by injection material, and there were no large anastomotic channels discernible.

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Atherosclerosis is the most frequent etiology, but in a very few cases, arteritis due to syphilis, rheumatic fever, systemic infections, or thromboangiitis obliterans may be responsible. Acute myocardial infarction may be the first clinical manifestation of coronary atherosclerosis when a single area of atheromatosis in an otherwise quite normal coronary arterial tree becomes the site of a fresh thrombus (Figure 9)

CASE 37-2, W. G., MALE, 50 YEARS

Close supervision for nine years because of gastrointestinal complaints, paroxysmal auricular tachycardia, four years, no congestive failure, angina pectoris, eleven days, coronary thrombosis, myocardial infarction, and death

Narrowing of left anterior descending and left circumflex arteries; freshly deposited thrombus completely occluding left circumflex artery; myocardial infarction and subsequent rupture of the heart

The patient had no complaints until 48 hours after admission when she suddenly collapsed and died while straining on a bedpan

Necropsy The heart weighed 376 gm. A fresh through-and-through infarction was found at the base of the left ventricle with rupture through the infarction producing pericardial tamponade All main coronary arteries showed atherosclerosis with moderate narrowing. An old complete occlusion was found in the posterior descending branch of the right coronary artery, the distal portion of which was filled with blue mass by collateral channels from the left coronary, in this area a slight amount of microscopic myocardial fibrosis was found. A large branch of the left circumflex coronary artery was occluded by a fresh thrombus the distal portion of this vessel was uninjected with mass, and the area of fresh myocardial infarction previously supplied by this vessel showed no collateral circulation.

In most instances, acute myocardial infarction occurred without relation to effort or other discernible event. Occasionally, in the presence of a previously compromised coronary circulation, special conditions which increase the work of the heart or reduce coronary flow temporarily may precipitate an acute infarction without an acute coronary occlusion. In some persons one or more of the following precipitating factors were evident unusual prolonged exertion, insulin hypoglycemia, concussion or trauma to the precordial area, shock consequent to operation, paroxysmal tachycardia, hemorrhage, or other causes. The small epidemics of acute myocardial infarction reported following every snowstorm offer examples of this type every winter.

In these times, when early ambulation is practiced following acute myocardial infarction and bed rest is regarded with abhorrence as old-fashioned, it may be well to summarize the chronology of the healing process in an acute myocardial infarct (13) Necrosis of the muscle and infiltration by polymorphonuclear leukocytes are the important features of the first week. Removal of the necrotic muscle and replacement by connective tissue predominate during the next five weeks. Collagen begins to be laid down by the newly formed connective tissue in the second week It gradually increases in amount, becomes more dense, and reaches its maximum in about three months This general time sequence is modified by the size and position of the infarct and by the state of the remaining coronary circulation Small infarcts may be almost completely healed after five weeks Large infarcts usually are not completely healed until two to four months have passed.

In approximately half of the patients, however, angina pectoris, mild or severe, has been present. Such a case is the following (Figure 10):

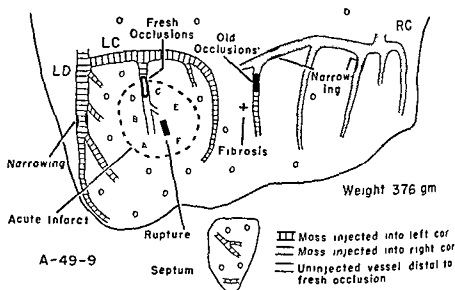


Figure 10. Diagram of injected heart of case 49-9

CASE 49-9, I N, FEMALE, 71 YEARS

Arterial hypertension twenty years Angina pectoris three years Prolonged cardiac pain nine and seven days before death Sudden collapse and death on second day of hospital admission

Necropsy showed myocardial infarction with rupture of left ventricle Old complete occlusion right coronary artery, narrowing of left anterior descending artery, fresh occlusion in left circumflex artery

I. N, a 71-year-old woman, had squeezing substernal pain one week before admission lasting two hours, accompanied by a choking sensation and cold sweat. Hypertension of 170/100 had been present for 20 years and occasional angina pectoris for three years A second episode of pain lasting one hour occurred five days before admission, but she remained up and about at home for five days. There were no other cardiac symptoms, but the patient entered the hospital because of anorexia, right upper quadrant pain, and occult blood in the stools

Physical examination showed pulmonary emphysema and basal rales The heart was enlarged, the sounds were normal and a few extrasystoles were heard. The liver was enlarged four fingers below the costal margin, but there was no peripheral edema The blood pressure was 150/100 Laboratory studies showed a leukocytosis of 12,450 and an elevated sedimentation rate of 1.4 mm per minute. An electrocardiogram, however, was normal.

angina pectoris and of acute myocardial infarction. They must not be advised, as in angina pectoris, to continue or reduce only slightly their usual activities, nor, on the other hand, should they be confined to bed for long periods of time as in acute myocardial infarction. Patients with prolonged cardiac pain should be observed closely for seven to twelve days in order to determine whether they exhibit the clinical characteristics of coronary failure and to be certain that the attack of pain is not the preliminary warning to be followed after some days by an attack of acute myocardial infarction, a sequence that has been termed "preliminary pain" or "impending acute coronary occlusion" (15, 16). If continued observation indicates an attack of uncomplicated acute coronary failure, the patient may be permitted to assume gradually increasing activity, sitting up in a chair after approximately one week and then becoming ambulatory

Summary and Conclusions

In this survey, I have covered some of the chief aspects of our knowledge of the coronary arteries and the coronary circulation which have direct clinical implications

1 Some of the unique *physiological* characteristics of the coronary circulation have been pointed out

2 In the normal heart, the coronary arteries are *functionally* end arteries Watery injections, however, reveal anatomical fine anastomotic communications between the coronary arteries measuring less than 40 microns But they are of limited functional significance in obviating the untoward effects of sudden coronary narrowing or occlusion

3 Complete occlusion or considerable narrowing of one or more coronary arteries may exist without giving rise to any clinical signs or symptoms and without having produced myocardial damage.

4 The apparent inconsistency between the presence of long-standing obstructive arterial lesions and the absence of significant pathologic or clinical evidence of myocardial damage is dispelled by the demonstration of a collateral circulation which serves as a by-pass in relation to the obstruction in each of these hearts

5 The pathologic and physiologic substrate of angina pectoris, coronary failure, and acute myocardial infarction have been discussed

6 In all three of the discussed syndromes, i e , angina pectoris, coro-

The pathologic and clinical events in the first two months following acute myocardial infarction have an important bearing on the occurrence of cardiac rupture. Rupture of the heart was responsible for 10 per cent of the deaths of our patients who died during an attack of acute myocardial infarction. A study of the data on the through-and-through necrosis responsible for rupture revealed that persistent hypertension and effort were the two most important etiological factors associated with this catastrophe.

Observations in Patients with Coronary Failure

In certain cases, a perplexing diagnostic problem confronts the physician when cardiac pain more prolonged than that consistent with angina pectoris occurs, but, on the other hand, the clinical evidences of myocardial necrosis, such as fever, leukocytosis, increased sedimentation rate, progressive electrocardiographic changes over a period of days, and the other recognized clinical features of acute myocardial infarction, are not observed. The hearts of such patients did not show myocardial infarction on the occasions when they were examined post mortem, one or more areas of coronary obstruction were present, however (14). In accordance with the concept that cardiac pain is due to relative myocardial ischemia, such attacks usually were coincident with increased demands on the heart, such as paroxysmal heart action, emotion, or exertion, whereas, in other instances, decreased coronary blood flow following fall of blood pressure in shock was apparently responsible. In some hearts, fresh coronary occlusions or fresh areas of narrowing were present. The occurrence of pain reflects the absence or temporary inadequacy of compensatory collateral circulation These episodes of coronary failure differ from angina pectoris in the longer duration of the attack and in some instances in the altered characteristics of the pain. On the other hand, the signs of myocardial necrosis are absent. The clinical diagnosis of either angina pectoris or acute myocardial infarction would be erroneous. We have designated this intermediate syndrome of prolonged cardiac pain as coronary failure

The therapeutic management of episodes of this intermediate syndrome of acute coronary failure depends on clinical recognition and proper evaluation of the underlying physiologic and pathologic changes. The treatment of patients with coronary failure differs from that of

angina pectoris and of acute myocardial infarction. They must not be advised, as in angina pectoris, *to continue or reduce only slightly* their usual activities, nor, on the other hand, should they be confined to bed for long periods of time as in acute myocardial infarction. Patients with prolonged cardiac pain should be observed closely for seven to twelve days in order to determine whether they exhibit the clinical characteristics of coronary failure and to be certain that the attack of pain is not the preliminary warning to be followed after some days by an attack of acute myocardial infarction, a sequence that has been termed "preliminary pain" or "impending acute coronary occlusion" (15, 16). If continued observation indicates an attack of uncomplicated acute coronary failure, the patient may be permitted to assume gradually increasing activity, sitting up in a chair after approximately one week and then becoming ambulatory

Summary and Conclusions

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4 The apparent inconsistency between the presence of long-standing obstructive arterial lesions and the absence of significant pathologic or clinical evidence of myocardial damage is dispelled by the demonstration of a collateral circulation which serves as a by-pass in relation to the obstruction in each of these hearts.

5 The pathologic and physiologic substrate of angina pectoris, coronary failure, and acute myocardial infarction have been discussed.

6 In all three of the discussed syndromes, *i e* , angina pectoris, coro-

nary failure, and acute myocardial infarction, the underlying mechanism seems to be a relative disproportion between the requirements of the heart for blood and the supply through the coronary arteries The changes in the myocardium resulting from this disproportion depend solely on the extent and duration of the relative ischemia, not on the manner in which they are produced.

7. The absolute necessity for immediate and complete bed rest, sedation, reduction of excessively high cardiac rates, and other measures designed to reduce the work of the heart in the presence of prolonged cardiac pain is emphasized as a means of limiting the extent of myocardial necrosis or even preventing its development. Such a regimen also affords an opportunity for the development of a more adequate collateral circulation. Similar considerations would seemingly apply to patients in whom angina pectoris suddenly appears or when the frequency or intensity of the attacks suddenly increases

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Chapter 6

THE CLINICAL RECOGNITION OF CORONARY HEART DISEASE *

Robert L. Levy †

OVER NINETY per cent of the lesions which affect the coronary arteries are due to atherosclerosis, and it is with this group that the present discussion is concerned. Coronary heart disease occupies a dominant place in clinical medicine because of the large number of individuals involved, because it kills or impairs the efficiency of many who are in the most productive period of life, and because the pictures which it presents are so varied in their manifestations. It offers a challenge in that the fundamental mechanisms involved in the production of arterial degeneration are still imperfectly understood.

Historical Background

The earliest observations correlating advanced disease of the coronary arteries with serious illness were probably those of Théophile Bonet of Geneva (1) In 1700, he described the case of a middle-aged poet who died shortly after a paroxysm of dyspnea which may well have been an anginal seizure At autopsy there was found ossification of the coronary arteries and these were almost completely occluded.

There are two prominent landmarks in the development of our knowledge. The first is the description of angina pectoris by William Heberden in 1768 (2) Heberden, however, was not aware that the chest pangs which he described were connected with the coronary arteries. It was Jenner who pointed out this relationship several years later The second is the account of coronary thrombosis by James B. Herrick as given in his papers published in 1912 and 1919 (3, 4). Herrick's story of his

* Presented October 9, 1951, at the Twenty-fourth Graduate Fortnight of The New York Academy of Medicine

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efforts to acquaint the medical profession with the clinical features of coronary heart disease is told in his recent autobiography which he has called *Memories of Eighty Years* (5). It is characteristic of the reluctance with which new viewpoints so often are received

"In 1912," he says, "my paper on 'Clinical Features of Sudden Obstruction of the Coronary Arteries' appeared, based on a case of coronary thrombosis in which I had made an ante mortem diagnosis. Recognizing the radical nature of the views I held, which led me to conclude that this condition was not, as was then the belief, merely a pathologic curiosity but in reality a clinical entity with symptoms that often made it possible to diagnose it during life, I postponed publication for some time until, by search of the literature and further observation, I had reached conclusions that seemed to me justifiable and sound. The paper when read in 1912 before the Association of American Physicians aroused no interest It fell like a dud" It was seven years later, after the publication of his second paper, to quote further, that "physicians in America and later in Europe woke up, and coronary thrombosis came into its own, to become later a household word translated by the layman into 'heart attack.'"

It has always seemed to me that the contribution of Ernst von Leyden of Danzig, published in 1884 (6), has not been given the recognition which it deserves Leyden was a good pathologist and an excellent clinician He divided coronary sclerosis, with respect to its effects, into four groups 1) sclerosis without disturbance of heart function, that is, without symptoms, 2) acute thrombotic softening or hemorrhagic infarction, 3) a chronic form leading to disseminated or diffuse fibrous degeneration of the myocardium and, in some instances, to ventricular aneurysm, 4) a combined form in which is found an old fibrotic process as well as acute thrombotic softening. He also described the group of acute cases with sudden death It is surprising that this approach, which resembles so closely our current views, was relatively ignored even in Germany where these and other pertinent observations had been made.

Recognition in a Modern Hospital

Eighteen years ago an attempt was made to trace the development of awareness of the coronary problem in the wards and autopsy room at the Presbyterian Hospital in New York by charting and comparing the

incidence of clinical and pathologic diagnoses during the period from 1910 to 1931 (7). These observations, published in 1934, have now been extended to cover the period from 1910 to 1950, and since 1930 cases in various affiliated institutions in the Columbia-Presbyterian Medical Center have been included. The figures obtained during a year have been tabulated at 5-year intervals. In this way certain facts and trends have become apparent (Table I).

TABLE I

Clinical and Autopsy Incidence of Coronary Diagnoses at Five-year Intervals, Columbia-Presbyterian Medical Center, 1910–1950*

Year	*Total hospital admissions*	*Clinical coronary diagnoses*	*Total autopsies*	*Autopsy coronary diagnoses*	*Rate of clinical coronary diagnoses per 1000 admissions*	*Per cent of total autopsies with coronary diagnoses*
1910	4,038	—	111	11	—	9.9
1915	3,843	2	113	21	0 5	18 6
1920	4,300	11	126	43	2.6	34 1
1925	4,092	19	117	44	4.6	37.6
1930	14,788	107	231	68	7.2	29.4
1935	17,134	132	304	92	7.7	30 3
1940	19,878	173	292	111	8.7	38 0
1945	21,427	213	283	112	9.9	39 6
1950	25,474	228	295	141	9.0	47.8

It is clear that in these data are inherent certain errors which cannot be avoided. There is variation in the character of the hospital population with respect to disease, age, and sex. There is variation also in the composition of the autopsy material with respect to the types of diseases observed. The slight changes in the figures of Table I, due to the modification of the hospital population by the later inclusion or exclusion of certain of the affiliated institutions caring for special types of cases, may well have been due to chance variations For estimating the frequency with which the clinical diagnosis of coronary disease was made, only those records were used in which there was specific mention of coronary

* The composition of the hospital population varied somewhat during the period covered Ward, semiprivate, and private patients are included from 1930 on, Sloane Hospital (with its newborn) is included From 1940 on, Eye Institute is included, but Babies Hospital, Neurological Institute, Orthopedic Hospital, and Mary Harkness Convalescent Home are excluded

involvement. In many instances it seems certain that, in the absence of manifest symptoms or signs, or because interest in some other condition was dominant, this diagnosis was not recorded in the final appraisal of the case. Such circumstances obviously would lower the figures for incidence. In the autopsy group all types and degrees of coronary lesions were included As was indicated in our previous publication, more than 93 per cent were arteriosclerotic.

The results, shown in the final two columns of Table I, have been reviewed to determine whether some of the fluctuations might be merely chance variations * It is noteworthy that the term coronary disease does not appear as a final diagnosis in any history in 1910 In going over some of the old files, one finds reference to angina pectoris but none to coronary thrombosis or myocardial infarction. Such cases were designated as chronic myocarditis, cardiac insufficiency, or, occasionally, pyrexia of unknown origin. This latter group was shown at autopsy to represent instances of cardiac infarction with fever. The general trend in frequency over the entire period shows a statistically significant increase. The relationship of sudden increases to the publication of Herrick's observations is of considerable interest. In 1912 his first paper appeared Although generally neglected, his observations made some impression at the Presbyterian Hospital because the diagnosis of coronary disease was made twice during the year 1915. In 1919, after publication of his second paper, there was a larger upward jump in the rate of clinical diagnosis from 0 5 to 2 5 per thousand admissions. From then on, there occurred a gradually progressive increase in the number of coronary diagnoses, although the change from year to year was not statistically significant. However, the difference between the figure of 4 6 in 1925 and of 9.0 in 1950 is significant During the past two decades there has been no important increase

The pathologists recognized and recorded coronary diagnoses even in 1910 Again the trend during the next 40 years is statistically significant. As was the case among the clinicians, the pathologists were made more aware of the importance of the coronary arteries in relation to the clinical features of disease after Herrick's first paper, and there is a rise from 9 9 per cent in 1910 to 18 6 in 1915 Again, after Herrick's second

* Miss Ann Baranowski, of the School of Public Health of the Faculty of Medicine of Columbia University, furnished helpful advice in this review

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concern The one common denominator at the basis of the manifestations of all coronary disease is coronary insufficiency. This may be defined as the disorder in which the amount or quality of blood is inadequate to meet the demands of the myocardium if it is to function as an efficient pumping mechanism Oxygen is essential for effective muscular contraction; hypoxia or anoxia of the myocardium is the fundamental cause for the disturbances produced These may result from various anatomic or physiologic lesions

In Figure 11, there is presented a schema which, it is believed, includes the various clinical features of coronary heart disease on the basis of coronary insufficiency. It offers a simple concept and one in which there is unity of cause

Coronary insufficiency may be acute or chronic. In the *acute form*, there may be no recent occlusion and no recent infarction In this variety pain is the most common symptom Discomfort may be brief, of the anginal variety, or it may be more prolonged, lasting 20 minutes or more and yet not followed by cardiac infarction This is the type of pain intermediate between the discomfort of an anginal attack and that associated with occlusion and infarction It has been designated by Blumgart (9) as "coronary failure", but merely because of its duration, it does not merit a name of its own There are certain pain equivalents, such as weakness, sweating, or a sense of pressure or tighmess across the chest Discomfort may be referred to the abdomen and regarded as a digestive disorder At times pulmonary edema or paroxysmal dyspnea will usher in an attack Focal anoxia may initiate an arrhythmia Sudden death in the presence of an impaired coronary circulation may follow some unusual exertion or emotional experience; it is to this type that the term "acute, fatal coronary insufficiency" has been applied (10).

Recent occlusion of a vessel, whether by a thrombus or atheroma, or marked stenosis may cause fresh infarction Under these conditions, pain is apt to be more prolonged and not infrequently is associated with nausea or vomiting Again there may be substitution symptoms, such as mild substernal pressure, general weakness, sweating about the head and neck, or digestive disturbances. Pulmonary edema sometimes is observed following *sudden closure*, and congestive failure may follow when the collateral circulation is inadequate to nourish the remaining uninjured heart muscle Occlusion may be without discomfort and some-

paper, there is a significant increase from 18.6 to 34.1. From then on, the variations are only of borderline significance or not significant at all

In short, during the past 40 years the number of clinical diagnoses of coronary heart disease has increased in frequency in a large university medical center. Greater diagnostic skill probably was largely responsible, particularly in the earlier years. The diminution in the number of patients with acute infectious diseases and the aging of the population, as well as other changes in the character of those admitted to the hospital, are factors which must also be considered. Although prior to 1920 there is a trend upward of the incidence found at autopsy, the slope of the curve is not as sharp as that depicting the frequency of clinical diagnoses In fact, in the later years, the incidence appears to be essentially constant. Within the limitations of the character of the autopsy material, it seems that the clinicians, with the aid of more accurate methods of diagnosis, are now recognizing conditions during life which have for a much longer period been apparent to the pathologists.

No claim is made that these figures are generally applicable and represent an over-all picture. They are, however, probably more reliable than any which could be obtained from death certificates A comparable study was recently published by Morris (8), who analyzed necropsy records of the London hospital where the coronary arteries, as well as the myocardium, have been routinely examined since 1907 Some 6000 records from this hospital were studied from that date to 1949. They showed a sevenfold increase during this period in the number of cases of coronary heart disease. Morris concluded that coronary sclerosis and myocardial infarction, rare before World War I, have since become common and that this increase represents a rising incidence rather than *better recognition.* Our own observations suggest that both factors probably are concerned, but tend to place the preponderant emphasis on greater accuracy in diagnosis

Clinical Recognition

The diagnostic approach to any group of diseases requires a logical classification for proper understanding. Atherosclerosis of the coronary arteries causes a variety of pathologic lesions, both in the vessels and in the heart muscle. From the point of view of the physician who treats the patient, it is the resulting disturbances in function which are the chief

From the point of view of the attending physician, the most important diagnostic problem is to determine whether recent infarction has taken place, for upon its presence or absence will depend the general management of the patient. The criteria for the diagnosis of infarction are now well established, but it is proper to emphasize again that the picture of coronary heart disease is varied and that its recognition sometimes presents real difficulties. There is no classic pattern.

Diagnostic Aids

Sclerosis without recent occlusion There is no form of examination which is as important as the taking of a good history. This has been said many times but still is not sufficiently appreciated. The physician who is responsible for the care of the patient should be the one to hear from the sufferer's own lips his history of discomfort. In many cases such an account, if skillfully obtained, suffices for diagnosis, it may be the only evidence obtainable, for the physical examination and all special tests may prove to be negative

On physical examination, the presence of cardiac enlargement, in the absence of hypertension, valvular disease, or other manifest cause, should always arouse suspicion. This should be confirmed by x-ray or orthodiagraphic examination Changes in the form of the electrocardiogram may afford graphic evidence of myocardial injury. Of particular importance are bundle branch block, significant T-wave negativity, and arrhythmias, particularly auriculoventricular block or auricular fibrillation or flutter It should always be kept in mind that alterations in the electrocardiogram are not etiologically specific and that they must be interpreted in terms of the clinical picture as a whole, *it is not possible to make a diagnosis of coronary heart disease on the basis of the electrocardiogram alone*

In recent years, the ballistocardiograph has become of increasing interest as a diagnostic tool. In its original forms, whether damped or undamped, it is a cumbersome and expensive instrument requiring considerable technical skill for its proper manipulation The correct interpretation of ballistocardiographic records likewise demands experience and special knowledge. In the hands of Starr and others such tracings have afforded early evidence of myocardial dysfunction and have suggested coronary insufficiency at a time when other methods failed to

times occurs "silently," particularly in the old and debilitated. Sudd closure may initiate ventricular fibrillation and be followed shortly b sudden death.

In the *chronic form* there is no recent occlusion and no recent infarctio The common finding is myocardial fibrosis with or without heal

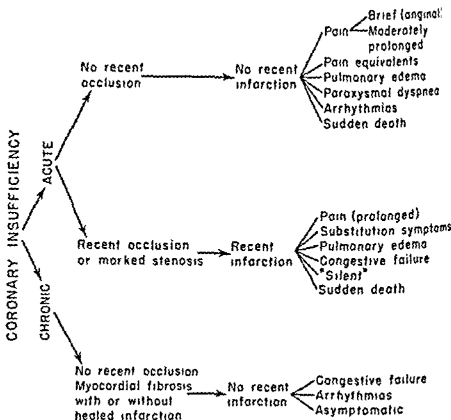


Figure 11 Clinical features of coronary insufficiency

infarction. This is the condition to which formerly was applied the term "chronic myocarditis." The heart is usually enlarged, and congestive failure is frequent. There may be arrhythmias of various sorts, including premature contractions, auricular fibrillation or flutter, or varying degrees of auriculoventricular heart block. Sometimes the condition is asymptomatic and is discovered only when the electrocardiogram shows bundle branch block, significant T-wave negativity, or other evidence of old myocardial injury.

with a burning sensation behind the sternum This occurred only on exertion. Electrocardiograms and x-rays of the chest taken then, were said to have been negative He continued at work for a year although the sensation recurred At the end of a year, another x-ray was made, and he was told that his heart was enlarged Aspirin and bicarbonate of soda appeared to afford some relief. He was sent to Arizona for six months but returned to New York unimproved For the two months prior to admission he complained of attacks of knifelike pain in the

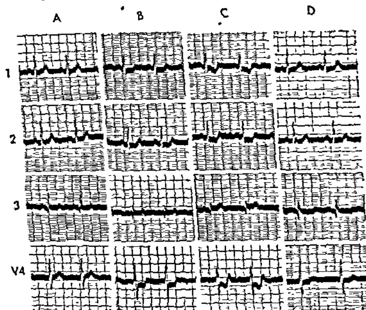


Figure 12 Anoxemia test (*A*) control, (*B*) after breathing 10 per cent oxygen for 5 minutes, (C) after 20 minutes of hypoxia, (*D*) 5 minutes after breathing 100 per cent oxygen for 1 minute.

right shoulder which sometimes radiated to the right ring finger These occurred chiefly in the evening before retiring X-rays of the gallbladder revealed no stones and no disturbance in function He stated that nitroglycerin relieved the pain in his right shoulder but did *not* affect the discomfort in his chest His story rambled and was confusing

Examination showed no cardiac enlargement on physical examination or by x-ray There was a short, blowing systolic murmur at the apex The blood pressure was 135 mm Hg systolic, 90 diastolic The blood count was normal The venous pressure was 78 mm of water The circulation time, by the Decholin method, was 20 seconds X-rays of the gastrointestinal tract revealed no abnormalities There were osteoarthritic changes in the thoracic spine, especially

indicate its presence (11). Results obtained with the use of smaller instruments, such as that devised by Dock (12), should, for the present, be accepted with caution. These devices are more susceptible to oscillations produced outside the body than are the table models. Whether records obtained with the smaller machines are wholly reliable is still open to question. It seems likely that a relatively simple and accurate ballistocardiograph will be developed in the near future. The practical usefulness of such an apparatus is still to be determined.

In a small group of cases, the history and examination leave the physician in doubt as to whether he is dealing with a coronary problem Under these circumstances, two special stress tests have been devised The two-step exercise test of Master (13) is comparatively simple to perform. The chief objections to it are that 1) criteria of a positive response are not well defined and 2) false positives occur (14). These, in our opinion, are serious faults. Furthermore, we are not convinced of the claim made by the sponsors of this test that a negative result excludes coronary insufficiency.

Our own studies have been concerned more particularly with the anoxemia test, during which the patient is made to breathe, at the normal rate of respiration, a mixture of 10 per cent oxygen and 90 per cent nitrogen (15, 16, 17). This test has now been used extensively both in this country and abroad and, with the exercise of the simple precautions which have been outlined, is entirely safe. Anoxia is quickly reversible because 100 per cent oxygen can be given at once. It should be used only in cases in which the diagnosis is in doubt The criteria for a positive effect have been clearly stated and in thousands of tests performed in many clinics have been found to be valid. A recent report by Nylin (18), of Stockholm, presents favorable results in 1130 tests. In the light of a large experience, we can reiterate the statement that a positive test is a sign of coronary insufficiency, on the other hand, a negative test does not rule out the possibility that lesser degrees of coronary insufficiency may be present

The following case report relates an instance in which the test was a decisive factor in diagnosis

C. G (Unit No 842455) was a jewelry salesman, 58 years of age, and was referred from another hospital because of pain in the chest and shoulders, of one month's duration. However, the present illness really began five years previously

with a burning sensation behind the sternum This occurred only on exertion Electrocardiograms and x-rays of the chest taken then, were said to have been negative He continued at work for a year although the sensation recurred At the end of a year, another x-ray was made, and he was told that his heart was enlarged Aspirin and bicarbonate of soda appeared to afford some relief. He was sent to Arizona for six months but returned to New York unimproved. For the two months prior to admission he complained of attacks of knifelike pain in the

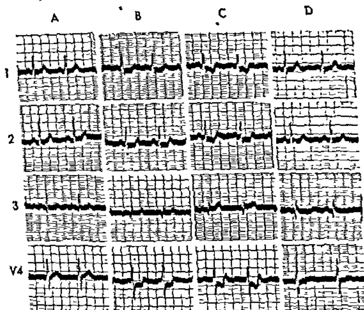


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on the right side. An electrocardiogram, including precordial leads, was normal

The anoxemia test was strikingly positive, as shown in Figure 12. There were changes in both the RS-T segments and in the T waves. The patient did not complain of discomfort during the test but at its conclusion said that after 10 minutes of hypoxia he experienced pain in the upper back on the right side and across the right chest. The oxygen saturation of the blood was determined during the period of hypoxia by the Millikan oximeter. The control reading was 97 per cent, after 5 minutes, 78 per cent, after 20 minutes, 75 per cent; 5 minutes after breathing 100 per cent oxygen for 1 minute, 98 per cent.

Recent observations by Gofman and his associates (19) indicate that variations in the patterns of lipoprotein in the blood serum, as studied with the ultracentrifuge, may reflect varying degrees of error in lipid metabolism. A strong positive correlation has been demonstrated between elevation of the larger "Sf 10–30" class of lipoproteins and the rate of development of atherosclerosis. Chemical changes in the blood and tissues may well furnish clues relating to the origin of arterial degeneration, and it seems possible that such changes may be employed diagnostically to detect the basic metabolic fault in its early stages at a time when it can be retarded or reversed

Summary

The existence of lesions in the coronary arteries has been known for several centuries, but the correlation between the pathologic changes in these vessels and the clinical manifestations caused by them were slow to be recognized It is only in the past thirty-five years that the medical profession has become familiar with the problems of coronary heart disease and aware of their importance There has been an increase in the incidence of the diagnoses of coronary disease during this period, both at the bedside and at the autopsy table, as indicated by a survey of the records at the Columbia-Presbyterian Medical Center from 1910 to 1950. The upward trend in the frequency of clinical diagnosis has been greater than that in the autopsy series, probably due in large part to the development of greater diagnostic skill, however, there appears to have been a significant increase as found at autopsy, most marked during the decade 1910 to 1920

The clinical manifestations of coronary heart disease are due to a functional disorder which, in all instances, is coronary insufficiency. A schema has been presented on the basis of which these features, acute

or chronic, with or without infarction, may be viewed as effects of a disproportion between the amount of blood available for the myocardium and the work which the heart is called upon to perform

Certain diagnostic aids have been discussed and their value has been appraised The solution to the problem of coronary heart disease is to be found in discovering the cause of atherosclerosis, and eventual understanding of its nature will point the way to more effective therapy and, of even greater importance, to measures for prevention.

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Chapter 7

THE IMPORTANCE OF CARDIAC ARRHYTHMIAS*

Louis N. Katz †

IT IS A PRIVILEGE to participate in the 24th Graduate Fortnight, which represents the joint efforts of The New York Academy of Medicine and the New York Heart Association, a most important affiliate of the American Heart Association.

The subject of the irregularities of the heart is an old one but it needs review. It constitutes an important area of clinical medicine that the physician needs to know thoroughly. Cardiac arrhythmias are divided into 1) disturbances in impulse initiation, and 2) disturbances of impulse conduction (1)

The impulse for the heartbeat may arise in the primary pacemaker, the sinus node, or in some ectopic pacemaker outside the sinus node. When it arises in the sinus node, it may be a regular sinus rhythm, with a regular periodicity somewhere between 60 and 100 beats per minute It may be faster than this, sinus tachycardia. It may be slower, sinus bradycardia It may be irregular in its rhythm, sinus arrhythmia. The irregularity in sinus arrhythmia is often obviously associated with respiration and is therefore called phasic, sometimes it is not and is then known as nonphasic The impulse in sinus arrhythmia may come from one focus or it may wander from one part of the node to another. The latter is known as a wandering sinus pacemaker.

When the pacemaker is outside the sinus node, such an ectopic rhythm may be a passive one, occurring when there is depression of the primary pacemaker or blockage of its impulse. This may appear as a persistent nodal rhythm (of the A-V node) or it may be an occasional nodal escape;

* Presented October 15, 1951, at the 24th Graduate Fortnight of The New York Academy of Medicine

† From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Illinois.

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it may be in the form of an idioventricular rhythm associated with complete A-V heart block. Rarely, it may be a ventricular escape. It may be a wandering of the pacemaker between the sinus pacemaker and the secondary one, the A-V node, a perfectly normal phenomenon.

Ectopic rhythms may be active, the most common being premature systoles. These ectopic rhythms may be of A-V nodal, auricular, or ventricular origin, rarely of sinus node origin. They may be in the form of paroxysmal tachycardia, supraventricular or ventricular in origin They may be in the form of chaotic heart action. More commonly they are auricular flutter or auricular fibrillation Rarely, they may be ventricular flutter or fibrillation, most often a terminal event, but on rare occasions, paroxysmal.

In the case of disturbances of impulse conduction, one should distinguish between the expression of the normal physiology of the conducting system, that is the phenomenon of the normal refractory period, and actual depression of the conduction process with abnormal prolongation of the refractory phase Since the heart must beat intermittently if blood is to be pumped, it is obvious that its inability to respond again immediately after stimulation is valuable. This is due to the presence normally of a long refractory period Should a second impulse reach a part of the heart during such a refractory state then it will not be transmitted at all or it will be delayed in its transmission. This phenomenon is called isolated interference (when one beat is affected) or dissociation (when several beats are affected in succession)

Interference and dissociation are to be distinguished from heart block. In heart block the transmission of the impulse is delayed or prevented because of disease of the heart which leads to an abnormal prolongation of the refractory period Such block may be between the sinus node and the auricle (S-A block), this is usually vagal in origin and most often due to digitalis. It may be within the auricles (intra-auricular block), which is recognized only in the electrocardiogram by irregularities and prolongation of the P wave It may be between the auricles and ventricles (A-V block) and appears in many varieties. It may be within the ventricles, intraventricular block or bundle branch system block, involving either the right bundle branch system, the left bundle branch system, or both, besides the isolated and focal varieties. Alternans of the heart may be considered, as a first approximation, to be a focal form of

heart block of the 2 to 1 variety. A different form of conduction disturbance is the phenomenon known as Wolff-Parkinson-White syndrome, due to an anomalous rapid A-V by-pass, a congenital anomaly.

The statistical frequency of these arrhythmias may be gleaned from the experience of the Heart Station of the Michael Reese Hospital, the clientele of which is a mixture of private and service cases, in- and outpatients, of various racial origins It is therefore a fair cross section of urban practice In about 25,000 cases with 50,000 records there were about 14,000 instances of regular sinus rhythm About 3000 cases were sinus tachycardias, about 1000 were sinus bradycardia, and about 6000 were sinus arrhythmias, the vast majority being phasic.

There were about 200 instances of persistent nodal rhythm, about 100 instances of nodal escape and about 500 cases of wandering pacemaker. Premature systoles, which I believe we have all had at one time or another, occurred over 2000 times, the ventricular variety being by far the most common Paroxysmal tachycardias occurred over 150 times; however, their frequency is apt to be underestimated because the attack is usually over before a record is obtained.

Fibrillation of the auricles occurred about 1500 times, next in frequency to sinus arrhythmia and premature systoles as a cause of irregular beating of the heart Auricular flutter occurred about 100 times. Ventricular fibrillation was extremely rare

A-V heart block constituted something like 700 cases, the majority of which were not recognizable at the bedside but only on the electrocardiogram Other forms of block were not common except for intra-auricular and intraventricular block both diagnosed by the electrocardiogram.

I would like to stress the fact that the study of the cardiac arrhythmias is one of the best ways to learn about the physiological properties of the human heart I would recommend this exercise to all of you. It has been a matter of continuous wonder to me how much we can learn about the heart by unraveling the various arrhythmias.

From such an analysis of the arrhythmias and some animal experiments, we can appreciate the role of the specialized heart tissue in impulse formation and transmission.

The specialized heart tissue is of *two* varieties. There is the nodal tissue which excels in giving rise to the impulses which govern the heart-

beat. It is not nervous tissue, it is not embryonic tissue, but neomorphic muscular tissue. It consists of the sinus node, the A-V node, and islets of nodal tissue located in the auricles and in the ventricles, in the latter in close association with the second variety of specialized heart tissue, the Purkinje system. The Purkinje system is primarily a rapid transit system for the ventricular myocardium. This tissue too is neomorphic. There are sufficient observations in man to substantiate the presence and importance of these two specialized muscular systems.

The physiology of clinical arrhythmias is still a matter of great current interest and lively concern. This can be illustrated by several examples.

1. I have recently reviewed a record which the late Dr. W. W. Hamburger had obtained in the 1920's, at that time it was considered a bundle branch block. It was obviously an instance of the Wolff-Parkinson-White syndrome. This case, recently reported by my associates Malinow and Langendorf (2) was still found to have the same condition some twenty years later He had had a history of paroxysmal tachycardia for years, but had no organic heart disease and was clinically well. He simply had this congenital anomaly of the conducting system. This is, to my knowledge, the longest lasting case on record

2. As a result of the recent studies of Scherf and Prinzmetal the circus movement theory of Lewis concerning auricular flutter and fibrillation has been called into question. In the early thirties, Brams and I (3) at the Michael Reese Hospital demonstrated that postfaradic auricular flutter and fibrillation in the dog with open chest persisted when the auricles were clamped or cut in the region over which the "mother ring" was supposed to be located. We used this as evidence against the simplified circus movement theory, and it is therefore pleasing to me to have this subject under scrutiny once again Recently also multiple precordial and esophageal leads have revealed isolated auricular waves of large size, which were going at rates of 300 or more, separated by quiescent periods in some cases of auricular flutter and fibrillation This finding also is difficult to reconcile with the simple circus movement theory. The mechanism of this type of arrhythmia is thus once again a matter of active study, and the final answer is still not available.

3. Recently a valuable addition to our therapeutic aids has been made available in the form of procaine amide. This we (4), like others, have

studied and found to be an excellent substitute for quinidine. In brief, it behaves like quinidine including its undesirable side action. It may be used in place of quinidine and should be especially valuable when there is an idiosyncrasy to quinidine.

I would like to point out that when we deal with the cardiac arrhythmias, we are dealing with disturbances in both rate and rhythm. In the case of paroxysmal ventricular tachycardia, for example, we often find intermittent periods of sinus rhythm between the periods of *rapid* ventricular beating. A glance at any record will also show how prolonged is the QRS duration of these ectopic beats. Thus, not only do the ventricles beat extremely rapidly but the time occupied in their stimulation is prolonged. This is a very wasteful method of beating mechanically, and so cuts down decidedly on the mechanical efficiency of the beat

Sometimes the rates of the human heart are *extremely rapid*. I have on occasion seen a ventricular rate in man persistently over 300. There are some birds like the humming bird *that* have rates over 1000 per *minute* At other times the human heart is extremely slow. I have seen cases with persistent rates as low as 18 per minute or even slower.

In auricular fibrillation the *rate is grossly irregular*. Sometimes the average rate is fast, approaching 300, at other times it is extremely slow. Complete A-V block *may* occur in auricular fibrillation, *sometimes* as a result of *too* much digitalis, and it *is possible* that the idioventricular pacemaker may fail to discharge leading to heart standstill. Or the digitalis medication may *cause frequent* premature systoles to appear, and this *carries the* hazard of leading *to runs of* such premature beats and even to ventricular fibrillation which is usually *terminal* Ventricular fibrillation is *only rarely reversible*, although I, like others, have seen such cases.

What is the importance of *arrhythmias*? The first thing I should like to *stress* is *that* arrhythmias are *often functional*, although they are, of course, sometimes due to organic heart disease. The thing the clinician should first assume when he finds a disturbed heart action, whether it be tachycardia, bradycardia, or *irregularity*, is that he is dealing with a functional disturbance, possibly a manifestation of psychosomatic disturbances He should, *of course, thoroughly* examine the patient to rule out organic heart disease but he should constantly remember that dis-

turbances in heart action are often functional and sometimes psychosomatic. Winton, Megibow, and I (5) have recently described an interesting case of paroxysmal auricular tachycardia definitely brought on by emotionally traumatic life situations. Almost any kind of arrhythmia may be caused by psychosomatic disturbances.

These psychosomatic disturbances in rhythm are in all likelihood the result of reflexogenic phenomena with the effector organ the heart, and the pathways involving the nerves regulating the heart. In addition hormones play a role, especially those of the adrenal medulla, in modifying the heart's behavior. Such patients have anxiety. The thing that I would like to stress is that in such cases the physician's handling of the case is of vast importance. If the doctor makes too much ado about the heart action, if he looks too long at the electrocardiogram, if he says, "Oh, you have an irregular pulse, it is just *nervousness*"—a word taboo to most patients—or casually remarks "forget about it," he may produce an anxiety neurosis, a "cardiac fixation." With the world full of people maladjusted in business or in family relations, a cardiac fixation is an excellent escape.

The palpitation associated with an irregular heart action is often disturbing even to well-adjusted people, and may become progressively more and more psychologically painful until it imitates the discomfort of an anginal attack. I have read an excerpt published by the late Soma Weiss of Boston from the diary of an intelligent medical student who was troubled with simple ventricular premature systoles. His description of the exquisite discomfort, the fright, the emotional unhappiness it created, even though he appreciated its benign quality, should warn us of the effect of irregular heart action upon less sophisticated persons who tend to be easily frightened by anything wrong with the heart. This discomfort I am sure all of you have experienced in one form or another at some time. Consequently I am sure you will be kind, solicitous, and careful with patients who have cardiac arrhythmias.

By and large, the treatment of arrhythmias is symptomatic. If they cause no trouble, they ordinarily require no therapy. With one or two exceptions there is no specific therapy for arrhythmias. Reassurance is important. Attacking the underlying disease, when it is organic will do a great deal to alleviate the large group of arrhythmias associated with organic heart disease.

It seems to me that the old-fashioned art of medicine is being lost in this era of instruments. A precise instrument does not necessarily make things more quantitative since the judgment still depends on human beings. We must therefore remember the entire patient when we are dealing with cardiac arrhythmias and plan our therapy accordingly. That is the true art of medicine.

There is specific treatment for some of the arrhythmias under certain circumstances. I would like to point out just one or two examples. Quinidine and papaverine are "soothing agents" for active ectopic rhythms. Papaverine is useful in this regard though not as potent as quinidine Pronestyl (procaine amide) has been recently added for this same purpose

In chronic coronary disease, in chronic coronary insufficiency, the exhibition of quinidine is extremely valuable when premature ventricular systoles are found It helps in these circumstances to prevent unexpected deaths, and it may help to avoid angina and heart failure.

Then there is the specific therapy of what we call the Stokes-Adams syndrome, complete A-V heart block. It should be called the Morgagni-Stokes-Adams syndrome There are several useful drugs for it. However, all I wish to point out at this time is that, in the presence of complete heart block, the convulsions and unconsciousness are many times due to inadequate circulation arising not from slow heart action, but by virtue of intermittent paroxysmal ventricular tachycardia Under such circumstances the exhibition of drugs like Adrenalin or some of the other sympathomimetic drugs may, as we found, clinically aggravate the condition of the patient instead of benefiting him. Therefore the first thing to do is to find out whether the mechanism causing the symptoms is due to slow ventricular action or to excessively rapid action

The bedside diagnosis of arrhythmias can be developed by training and perseverence We can diagnose many of the arrhythmias by looking at the jugular pulse, by palpating the heart and the radial artery, although the electrocardiogram is in almost all occasions the living autopsy with which to verify whether or not our judgments are correct As a matter of fact this is the way in which the diagnosis should be attempted, the electrocardiogram should not be used as the first line of evidence but to substantiate clinical judgment.

The prognosis of the arrhythmias is dependent upon the underlying

disease. Some twenty years ago, when I first became interested in this subject it was thought that persons with bundle branch system block had a definite prognosis—50 per cent of them would die in two years and 25 per cent in two months. Actually, when we analyzed this matter further, it became obvious that the statistics were due to the underlying diseases causing the block.

In the case of ventricular premature systoles of frequent origin, and in the presence of ventricular paroxysmal tachycardia, associated with organic heart disease, I am always fearful that unexpected death by ventricular fibrillation may occur. Nevertheless it is unwise to prognosticate solely from the arrhythmia. This is one of the ways in which electrocardiography has been improperly used.

Arrhythmias themselves lead to symptoms. They can lead to heart failure, both the forward failure variety with low output and the backward failure type with congestion. I am sure all of you have seen cases of paroxysmal tachycardia with cyanosis, congested veins, tender livers, and shortness of breath—all of which quickly disappear once the mechanism is broken. Angina pectoris is actually often induced in the presence of coronary disease or coronary insufficiency by rapid heart action or cardiac irregularity.

To understand how this comes about it is necessary to appreciate the volume curve of the ventricles. This is shown in Figure 13 and is based on the work of Wiggers and myself in 1922 (6). This expresses the way the dog's heart contracts, and it has been verified, in caricature, by the electrokymograph of the ventricular surface of the human heart (7a). The curve starts in diastole. When the impulse in the sinus node spreads to the auricles it causes them to contract and then relax (between VIII and IX and the homologous part of the curve ahead of I). The auricles contribute very little to filling; about 5 cc net out of the total of 60 cc at ordinary heart rates. Actually while they add 10 cc during their systole they "take back" 5 cc during their active relaxation. They are antechambers, not important pumps. The impulse reaches the ventricles at I, and they begin to contract, at first isometrically (between I and II). This is a presphygmic period or, as Wiggers has named it, the isometric contraction period, where the ventricular cavity does not change its volume and only its pressure rises. Then ejection begins. In this short period of time, from II to IV, the blood is ejected from the

ventricle (that is, all but the systolic residue of about 15 cc). Most of the blood is ejected during the rapid ejection period (II to III), and the small remainder in the reduced ejection period (III to IV). Diastole begins at IV with a short protodiastole phase (IV to V) and an isometric relaxation period (V to VI) during which the ventricle is relaxing isometrically, that is, without changing the volume of its cavity.

The point I wish to stress above all, which is not as widely appreciated

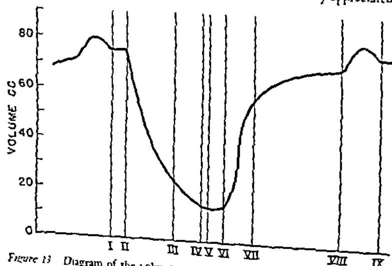


Figure 13 Diagram of the volume curve of one ventricular cavity of the human heart at an assumed rate of 80 *beats per minute*, a stroke volume of 60 cc, and a systolic residue of 15 cc, based on the studies of Wiggers and Katz (6) Discussed in the text

as it should be, is that most of the filling of the heart occurs in the rapid inflow phase (VI to VII), and that filling here is just as brusque, and the period of filling is just as short, as that of the rapid ejection phase. In other words, the heart fills with a rush over a short period and not deliberately and uniformly over the whole of diastole After the rapid inflow is the period of passive filling, diastasis (VII to VIII), due to the vis a tergo of the blood coming back to the heart. From this analysis it is obvious that the rapid emptying and rapid filling of the heart occupy only short periods of the cycle

With this background of the manner of the ventricular contraction and relaxation let us consider the effect of tachycardia. If we ignore

disease. Some twenty years ago, when I first became interested in this subject it was thought that persons with bundle branch system block had a definite prognosis—50 per cent of them would die in two years and 25 per cent in two months. Actually, when we analyzed this matter further, it became obvious that the statistics were due to the underlying diseases causing the block.

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varies with the square root of the cycle length, the heart spends more of its time in systole and less in diastole. That is, the heart as it speeds up works longer and rests less. Since the heart cannot go into oxygen debt to any appreciable extent (8), it is hard put to recover during its abbreviated diastole from the work done in its systole. This is another detrimental effect of tachycardia.

If one calculates the mechanical efficiency, i e., the work done over the energy utilized to do the work (using similar units), it can be shown that the efficiency of the heart as a machine goes down decidedly when it speeds up This too is a detrimental effect of tachycardia.

Thus, while tachycardia may be essential in fever, heart failure, and the like, for the heart to do its job, it is an inefficient and relatively costly way of doing it, and may lead by itself to troublesome circumstances, particularly in the presence of organic heart disease. It may hasten or aggravate failure of the heart and it may be the *trigger* causing angina pectoris.

Bradycardia also leads to circulatory disturbances. It has been demonstrated that the heart cannot increase its stroke volume, ordinarily by more than fourfold. That is, its stroke output cannot exceed approximately 250 cc. If the heart rate goes down markedly, the output per minute, the product of rates times stroke volume, may be adequate for rest, but when the patient gets up and around, it may become *inadequate* and forward failure may develop *Is it* surprising that under circumstances of emotional or physical stress, such a patient develops *the signs* of congestive heart failure or faints?

Two other facts about bradycardia need to be mentioned. One is that there is a large pulse pressure in bradycardia, and that in the presence of a roughened aorta, a diastolic murmur sometimes may occur. This murmur arises because eddies *are* set up, of a frequency audible to the ear, as blood moves backward to the heart over the roughened aorta immediately following systole. Velocity pulses in animals show the presence of this temporary ebb in the flow of blood in the aorta (9).

The large pulse pressure and this roughened aortic murmur may lead to the erroneous diagnosis of aortic valve regurgitation. It should be remembered that bradycardia, for reasons mentioned, may give the same two signs, especially in the older patient with aortic arteriosclerosis

The elevated systolic pressure in bradycardia should not be mistaken

compensatory mechanisms for the moment and assume that the only thing that will affect the output of the heart is the Starling effect, that is, that the stroke volume is a function of the end-diastolic volume of the ventricle, then it is obvious that as the rate speeds up from 80 beats per minute, the diastolic volume will decline and with it the stroke volume. At first these changes will be small because it will be the period of diastasis which is cut short. Hence the product of heart rate multiplied by stroke volume—which determines the minute volume—will increase. Thus up to rates of roughly about 150 or 160 or thereabouts the cardiac output per minute will tend to go up unless compensatory mechanisms prevent it. At first, therefore, tachycardia is beneficial in that the heart is able to pump out more blood per minute.

But when the heart rate gets faster than about 160, there is an encroachment upon the rapid inflow phase Hence diastolic volume and stroke volume decrease more rapidly, and soon the decrease in stroke volume is greater than the increase in heart rate and consequently their product, the minute volume output, declines. So tachycardia beyond a certain point cuts down the minute volume output unless compensatory mechanisms can make it up Tachycardia of marked degree leads to heart failure, and that is sometimes seen in paroxysmal tachycardia.

It is conceivable to imagine a rate so rapid that the heart starts its systole before filling begins Under these conditions all it can pump out therefore would be the systolic residue (of about 15 to 20 cc) Hence pumping would soon stop. That this can occur for a beat or so is known We have recently recorded the pressure pulse of the human aorta by passing a catheter into it (7b) and have noted ventricular premature systoles so early that even in the aorta there was no register of the beat of the heart.

Compensatory mechanisms will tend to make up for the deficiency of rapid heart action, but tachycardia beyond a certain point, despite such compensation, will become detrimental and can lead to circulatory insufficiency.

Tachycardia when excessive may also become detrimental because with increasing heart rate the coronary flow becomes less adequate and eventually coronary insufficiency develops This is revealed in the electrocardiogram as the posttachycardia syndrome, with its coronary-like S-T-T complex.

Furthermore, as the heart speeds up, because the duration of systole

varies with the square root of the cycle length, the heart spends more of its time in systole and less in diastole. That is, the heart as it speeds up works longer and rests less Since the heart cannot go into oxygen debt to any appreciable extent (8), it is hard put to recover during its abbreviated diastole from the work done in its systole. This is another detrimental effect of tachycardia.

If one calculates the mechanical efficiency, i e., the work done over the energy utilized to do the work (using similar units), it can be shown that the efficiency of the heart as a machine goes down decidedly when it speeds up This too is a detrimental effect of tachycardia.

Thus, while tachycardia may be essential in fever, heart failure, and the like, for the heart to do its job, it is an inefficient and relatively costly way of doing it, and may lead by itself to troublesome circumstances, particularly in the presence of organic heart disease. It may hasten or aggravate failure of the heart and it may be the trigger causing angina pectoris.

Bradycardia also leads to circulatory disturbances. It has been demonstrated that the heart cannot increase its stroke volume, ordinarily by more than fourfold That is, its stroke output cannot exceed approximately 250 cc If the heart rate goes down markedly, the output per minute, the product of rates times stroke volume, may be adequate for rest, but when the patient gets up and around, it may become inadequate and forward failure may develop Is it surprising that under circumstances of emotional or physical stress, such a patient develops the signs of congestive heart failure or faints?

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The large pulse pressure and this roughened aortic murmur may lead to the erroneous diagnosis of aortic valve regurgitation It should be remembered that bradycardia, for reasons mentioned, may give the same two signs, especially in the older patient with aortic arteriosclerosis.

The elevated systolic pressure in bradycardia should not be mistaken

for essential hypertension. Essential hypertension is not merely systolic hypertension but primarily a diastolic hypertension In bradycardia the elevated systolic pressure is associated with a lowered diastolic pressure.

Finally a few remarks about irregular heart action. In the ordinary case of auricular fibrillation with irregular pulse action the systolic and diastolic pressure are quite uneven from beat to beat. Actual recording with the Hamilton manometer shows variations of as much as 50 mm Hg between successive beats (10). In such instances it is difficult to get the actual blood pressure level.

When we consider irregular heart action we must realize we are dealing with an average rate, some beats are faster, others are slower than the average. At slow rates this irregularity has little significant effect but at faster rates it makes a real difference. Take the case of auricular fibrillation with an average ventricular rate of 130, actually some beats are occurring at the rate of about 80 and other beats are close to 180. The beats at the fast rates have all the disadvantages enumerated in tachycardia and so cut down the effectiveness of the heart as a pump. It is to this, and not to the supposed lack of the auricular contribution, that one must attribute the fact that auricular fibrillation is less effective than sinus rhythm. This is demonstrated by the ineffectiveness of some beats which give rise to the well-known pulse deficit in auricular fibrillation The difference between a patient with a heart rate of 130 and regular rhythm and one with the same rate and auricular fibrillation is the irregularity in the latter, the fact that many of the beats occur in quick succession, that some of them are ineffective and do not even get to the wrist. It is on this basis that auricular fibrillation with rapid ventricular rate can cause aggravation of heart failure and act as the trigger to angina pectoris.

In conclusion, it is obvious that cardiac arrhythmias constitute an important chapter of cardiology, the understanding of which will not only lead to satisfaction to the student of clinical medicine but, more important, to an improved management of the patient.

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Chapter 8

PATHOLOGIC PHYSIOLOGY OF MITRAL STENOSIS AND ITS SURGICAL IMPLICATIONS*

Lewis Dexter †

THE DEVELOPMENT of a direct surgical attack on narrowed mitral valves raises many questions as to its efficacy. Wilcox and Grace (1) have objected on theoretical grounds, believing that surgery could offer little or no benefit in the majority of patients with mitral stenosis. Harken and his associates (2, 3), Glover, O'Neill, and Bailey (4), Baker, Brock, and Campbell (5), and Prip Buus (6) have recently reported clinical improvement of their patients following direct valvular surgery The evaluation of operative results by clinical impression alone leaves much to be desired, however, because spontaneous changes frequently occur in the clinical course of these individuals. The advent of pulmonary vascular changes and of right ventricular failure, for example, may result in symptomatic improvement by relieving pulmonary congestion, yet marks the onward progression of the disease. Objective evaluation of mitral valve surgery is therefore not only desirable but necessary Baker, Brock, and Campbell (5) have studied the cardiac output and pulmonary arterial pressure in four cases after mitral valvulotomy, and we (7) have reported the postoperative changes in circulatory dynamics in six cases

This study reviews the pathological physiology of mitral stenosis as it relates to mitral valve surgery and analyzes the preoperative and early postoperative changes in circulatory dynamics in twelve patients with

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incapacitating mitral stenosis on whom mitral valvuloplasty was performed at the Peter Bent Brigham Hospital by Dr. Dwight E. Harken.

Pathological Physiology of Mitral Stenosis

A diagram illustrating the pathological physiology of mitral stenosis is shown in Figure 14. A detailed description of the points that follow have been published elsewhere (8, 9, 10, 11, 12). It is to be emphasized at the outset that this discussion applies to mechanical mitral stenosis wherein there is no concomitant active rheumatic carditis.

The normal mitral valve has a cross-sectional area of 4 to 6 sq cm. Methods have been developed by Gorlin and Gorlin (8) for accurately

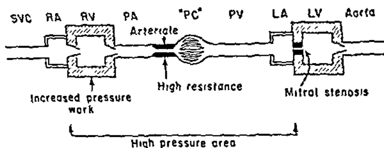


Figure 14. Diagram of pathologic physiology of mitral stenosis.

calculating the size of the orifice of the mitral valve during life in patients with mitral stenosis. In mitral stenosis, the orifice becomes narrowed and in the most advanced cases may be only 0.4 sq cm. Narrowing of the mitral valve orifice produces an obstruction to the flow of blood at a critical point in the circulatory system, i.e., at a point just distal to the capillaries of the lung. Between these capillaries and the mitral valve there are no valves or other important buffering mechanisms. Indeed, in many ways the pulmonary capillaries, pulmonary veins, and left auricle can be thought of as a single vascular compartment with pressures in all parts not differing by more than a few mm Hg. As the mitral valve orifice becomes narrower, it is obvious that if blood flow (cardiac output) is to be maintained at a normal level, pressure proximal to the mitral valve must increase. If pressure in the left auricle remains normal, blood flow must decrease. In mitral stenosis both occur, i.e., pressure in

the left auricle and lung rises and cardiac output decreases The pressure rise is predominant, however, and results in the symptoms of dyspnea, orthopnea, paroxysmal nocturnal dyspnea, pulmonary edema, and hemoptysis, these being the prominent symptoms of mitral stenosis and the ultimate cause of disability. These symptoms are attributable to a rise of pressure in the pulmonary capillaries to a level exceeding the osmotic pressure of plasma with the production of pulmonary edema These two compensations—a rise of pressure proximal to the valve and a decrease in the amount of blood flowing through the valve—are the only two important compensations that take place during the time that the mitral valve is becoming narrower and narrower. Not until late in the course, when the valve becomes about 20 per cent of normal (about 1 0 sq cm) does the third compensation appear

This compensation consists of narrowing of the arterioles and small arteries in the lung Histologically there is intimal proliferation and medial hypertrophy (13, 14) Physiologically, there is an increased resistance to blood flow through this segment of the lung which can easily be measured with the cardiac catheter (9, 15). There is considerable variation in patients with mitral stenosis of the same severity in the extent of this vascular resistance in the lung Some with tight mitral stenosis never develop important increases in resistance and these are the patients who have severe exertional dyspnea, orthopnea, hemoptysis, and attacks of acute pulmonary edema. These patients have hearts which are usually little if any enlarged, and there is no venous distension, hepatomegaly, or other manifestations of right ventricular failure (12). There are others who develop a moderate degree of pulmonary vascular resistance wherein there is a delicate balance between the resistances in the lung and at the mitral valve These patients have few respiratory complaints because the right ventricle, due to the increased pulmonary resistance, cannot pump blood into the lung any faster than it can comfortably escape through the mitral valve. These two areas of increased resistance—the lung and the mitral valve—result in a low fixed cardiac output so that the predominant symptoms are fatigue, exhaustion, weakness, tiredness, ennui. At this point, the heart is enlarged, but the right ventricle is usually still competent. In some individuals, the pulmonary vascular resistance becomes excessive, i.e., 15 to 20 times the normal The resistance to blood flow through the lung may become greater than

that at the mitral valve These individuals do not in our experience have episodes of pulmonary edema, but as in patients with severe cor pulmonale, there is excessive exertional dyspnea and orthopnea, the right ventricle becomes greatly enlarged and fails, with the appearance of venous distension, hepatomegaly, and edema.

The only clue to the mode of production of these pulmonary vascular lesions in mitral stenosis is that they make their appearance only late in the course of mitral stenosis when the size of the mitral valve is about 1.0 sq cm or less, at which point even at rest pulmonary edema impends. It has been postulated (15) that this chronic threat of pulmonary edema in some unknown fashion leads to the appearance of the vascular changes. We have considered it to be a compensatory mechanism successfully preventing the right ventricle from sudden surges of output, thereby preventing the flooding of the pulmonary capillaries with blood.

The importance of this pulmonary vascular resistance cannot be overestimated in modifying and influencing the clinical course of patients with mitral stenosis Before its appearance, respiratory symptoms become increasingly prominent as the valve becomes narrower. It is not until the pulmonary resistance becomes five to ten times the normal level that the transverse diameter of the heart by x-ray becomes increased and respiratory symptoms decrease, and ten to fifteen times the normal that the right ventricle fails grossly

Evaluation of Surgery

With these points in mind, it is obvious that relief of the stenosis itself may not necessarily result in clinical improvement of the patient unless the secondary changes in the lungs revert toward normal. As an amplification of an earlier report (7), an attempt will be made to answer the following questions based on the findings shortly after operation in twelve patients on whom mitral valvuloplasty for severe, incapacitating mitral stenosis has been performed.

1 Can the mitral valve orifice really be widened?
2 Is mitral insufficiency necessarily produced?
3. Does the cardiac output increase?
4 Do pressures in the pulmonary circuit fall?
5 Does the increased pulmonary arteriolar resistance return to or toward normal?

6. Does right ventricular function, as indicated by its filling pressure, return to or toward normal?

Material

Twelve patients with mitral stenosis subjected to mitral valvuloplasty (16) in the Peter Bent Brigham Hospital were all incapacitated, many leading a bed and chair existence, and were graded as Class III or IV according to the New York Heart Association classification. Studies were carried out a few days before operation and again between two

TABLE II

Circulatory Dynamics in Patients before and after Mitral Valvuloplasty

Patient	*Mitral valve stenotic area cm²*		*Cardiac index l/min/sq m*		*Pulmonary "capillary" pressure mm Hg*		*Pulmonary arteriolar resistance dynes sec cm⁻⁵*		*Right ventricular filling pressure mm Hg*		*Mitral regurgitation present*	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
M. McG	0.4	0.7	1.8	1.9	25	17	770	889	4	4	0	0
W. F.	0.5	0.9	1.8	2.8	23	20	1139	332	8	6	0	0
R. W.	0.6	1.2	2.7	2.2	34	11	274	441	9	4	0	0
E. D.	0.6	1.5	2.4	1.9	36	21	411	600	12	4	0	++
J. G.	0.6	1.5	2.1	2.9	34	17	400	200	10	2	0	0
L. L.	0.7	1.3	2.5	2.6	27	24	632	554	5	13	0	0
T. C.	0.7	1.7	2.9	3.3	32	14	488	254	7	7	0	0
C. F.	0.8	1.7	2.2	2.8	18	11	292	173	5	3	0	0
B. A.	0.9	1.6	3.6	3.8	32	19	569	364	0	5	0	0
N. W.	1.0	1.6	3.2	3.6	33	19	204	280	2	4	0	0
E. L.	1.1	2.3	1.4	1.9	24	10	1480	523	5	4	++	++
A. D.	1.3	1.9	2.0	2.3	37	26	103	178	8	4	++	++

and six weeks after operation. Mitral insufficiency was detected qualitatively from the contour of the pulmonary "capillary" pulse tracing and estimated semiquantitatively by means of hydraulic formulas (17, 18).

Methods

The methods have been described in detail elsewhere (9). In general they consisted of measuring cardiac output by the direct Fick principle and recording pressures with Sanborn electromanometers in the pulmonary "capillaries," pulmonary artery, right ventricle, right atrium,

and brachial artery. From these pressure and flow measurements, calculations by the formulas described elsewhere (6) have been made of the size of the mitral valve orifice, and the pulmonary arteriolar and total pulmonary resistances Estimates of the degree of mitral insufficiency, graded from one to four plus, have been based on the height of the v-wave in relation to the mean pulmonary "capillary" pressure (17, 18).

Results

Pertinent data will be found in Table II and Figures 15 through 19.

1 *Size of the orifice of the mitral valve.* In each patient, the mitral orifice was significantly increased in size by operation (Figure 15). In eight, the size of the orifice postoperatively was considered to be satisfactory, i e , greater than 1 5 sq cm. If the size of the valve orifice were the only problem in mitral stenosis, these eight patients could be expected to return to almost normal activity In R.W. and L L., an adequate size of the valve orifice was obtained, i e., 1.2 and 1.3 sq cm respectively. W F had an extremely elastic valve orifice which made finger fracture of the commissures difficult so that the resulting valve orifice measured postoperatively was only 0 9 sq cm The problem in her case was similar to that of trying to fracture a rubber band. Now that this problem is recognized, an appropriate surgical maneuver has been devised to overcome this difficulty In M. McG., the anatomical nature of the stenosis made enlargement of the orifice technically almost impossible.

2 *Mitral insufficiency.* Nine patients had mitral stenosis without insufficiency before operation None had mitral insufficiency postoperatively (Figure 15) Patients A D and E.L. had mitral stenosis and insufficiency before operation and, as nearly as could be judged, no definite change in their regurgitation either for better or for worse was produced by operation In one patient, E D., fracture of the valve commissure was carried forward unintentionally into the aortic leaflet so that some mitral regurgitation was produced. The dissection should have been carried to the annulus and no further or else into the minor leaflet This must be regarded as a technical error incident to efforts at improving leaflet mobilization Despite this one case, it is apparent that mitral valvuloplasty can relieve stenosis without producing regurgitation

3. *Cardiac output.* Cardiac output was not significantly different two

6. Does right ventricular function, as indicated by its filling pressure, return to or toward normal?

Material

Twelve patients with mitral stenosis subjected to mitral valvuloplasty (16) in the Peter Bent Brigham Hospital were all incapacitated, many leading a bed and chair existence, and were graded as Class III or IV according to the New York Heart Association classification. Studies were carried out a few days before operation and again between two

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	Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
M. McG	0 4	0.7	1.8	1.9	25	17	770	889	4	4	0	0
W. F.	0 5	0 9	1 8	2 8	23	20	1139	332	8	6	0	0
R W	0 6	1 2	2 7	2 2	34	11	274	441	9	4	0	0
E. D	0.6	1 5	2.4	1.9	36	21	411	600	12	4	0	++
J. G.	0 6	1 5	2 1	2 9	34	17	400	200	10	2	0	0
L L	0 7	1.3	2 5	2.6	27	24	632	554	5	13	0	0
T C	0.7	1 7	2 9	3 3	32	14	488	254	7	7	0	0
C F	0 8	1 7	2 2	2 8	18	11	292	173	5	3	0	0
B A.	0 9	1 6	3 6	3.8	32	19	569	364	0	5	0	0
N W	1 0	1 6	3 2	3 6	33	19	204	280	2	4	0	0
E L.	1 1	2 3	1 4	1 9	24	10	1480	523	5	4	++	++
A. D.	1 3	1 9	2 0	2 3	37	26	103	178	8	4	++	++

and six weeks after operation. Mitral insufficiency was detected qualitatively from the contour of the pulmonary "capillary" pulse tracing and estimated semiquantitatively by means of hydraulic formulas (17, 18).

Methods

The methods have been described in detail elsewhere (9). In general they consisted of measuring cardiac output by the direct Fick principle and recording pressures with Sanborn electromanometers in the pulmonary "capillaries," pulmonary artery, right ventricle, right atrium,

to three weeks postoperatively in the majority of patients (Figure 16). In W.F. and E.L. the cardiac output had increased appreciably, presumably due to the striking decrease of pulmonary arteriolar resistance. In J.G. and C.E., cardiac output rose significantly though not markedly. Baker, Brock, and Campbell (5) found little change in cardiac output in four cases studied two to three months after surgery. The failure of cardiac output to increase shortly after operation may be due to the "disuse atrophy" of the left ventricle which occurs in mitral stenosis and to the increased resistance in the arterioles of the lung, which tends to keep the output of the right ventricle depressed in mitral stenosis as well as in cor pulmonale (19, 20). The relative role of these two factors and the eventual level at which cardiac output will stabilize must await subsequent follow-up. Follow-up reports indicate clinically a progressive increase in exertional tolerance over the course of one to eight months at this writing, from which it is anticipated that the cardiac output gradually increases over the course of weeks and months.

4. *Pulmonary "capillary" pressure.* Since the valve orifice was enlarged and blood flow through it relatively unchanged, a striking fall of pulmonary "capillary" pressure occurred in eleven of the twelve patients (Figure 17). Baker, Brock, and Campbell (5) noted a fall of pulmonary arterial pressure postoperatively in three cases. The fall of pulmonary "capillary" pressure in our patients resulted in a relief of their pulmonary congestive symptoms which were their major cause of disability. In all but two cases, this pressure was well below the pulmonary edema level postoperatively. In W.F., pulmonary "capillary" pressure was little changed, but instead the cardiac output and blood flow through the valve had increased considerably. In A.D., severe mitral regurgitation was considered to be the cause of the failure of the pulmonary "capillary" pressure to fall to more normal levels. The dramatic fall of pulmonary "capillary" pressure postoperatively was reflected clinically by the impressive absence of dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion in the postoperative period.

5. *Pulmonary arteriolar resistance.* In eight patients there was no significant change in pulmonary arteriolar resistance two to three weeks postoperatively (Figure 18). In E.L. and W.F., the decrease of resistance was striking and was in excess of any possible error in the methods. In T.C. and J.G., less striking but significant reductions of the resistance

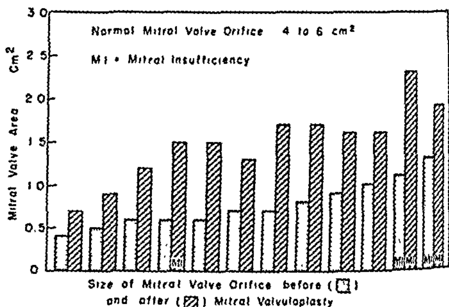


Figure 15

Cardiac Index liters/min/sq m

4

3

2

1

0

LOWER LIMIT OF NORMAL

MI

MI MI

MI MI

Cardiac Index before ( ) and after ( ) Mitral Valvuloplasty

Figure 16

were observed The marked fall of resistance in E.L. and W.F. so early in the postoperative period strongly suggests that part of the elevated arteriolar resistance preoperatively was due to functional vasoconstrictor activity and that the postoperative values for resistance represented the residual obstruction due to organic narrowing of the arterioles which is known to be present in severe mitral stenosis (13, 14). In two patients (B.A. and T.C), values for resistance returned almost to normal (160 and 131 dynes second cm^{-5} respectively) seven months

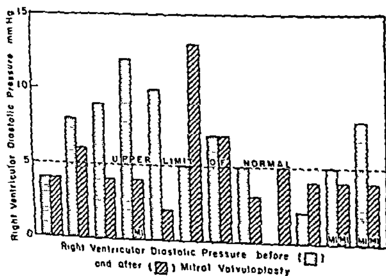


Figure 19

postoperatively Whether organic narrowing of pulmonary arterioles is reversible in all patients is not known and must await study of more cases

6 *Right ventricular function* Six patients had elevations of right ventricular diastolic filling pressure (Figure 19) In four of these patients, values were normal postoperatively, in one (W F) it had fallen slightly, and in one (T.C) it was unchanged In one patient (L.L.) there was a rise from 5 mm Hg preoperatively to 13 postoperatively. Active rheumatic carditis was suspected as the cause, although there were no other confirmatory manifestations. The general trend was clearly a reversion

Pulmonary "Capillary" Pressure mm Hg

40 35 30 25 20 15 10 5 0

PULMONARY EDEMA THRESHOLD

UPPER LIMIT OF NORMAL

MI MI MI MI MI

Pulmonary "Capillary" Pressure before ( ) and after ( ) Mitral Valvuloplasty

Figure 17

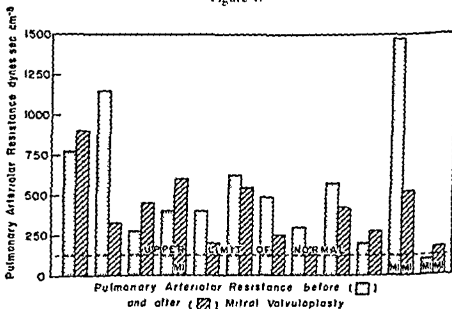


Figure 18

be anticipated to be higher in fibrillators, but it is these very patients who stand to receive the greatest benefit from surgery. The eventual effect of the operation on cardiac rhythm remains to be determined. At this writing, there is no evidence that chronic auricular fibrillation spontaneously reverts to normal sinus rhythm postoperatively.

The only five absolute contraindications to operation at this stage of evolution of the surgical procedure, in our opinion, are: 1) that the mitral stenosis is too mild, i.e., symptoms are not severe enough to keep the patient from a useful and productive life, 2) that there is a serious associated disease, e.g., tuberculosis, nephritis, etc.; 3) that bacterial endocarditis is present; 4) that active rheumatic fever is present; and 5) that other valve lesions are present in serious degree. The *recognition* of rheumatic carditis is difficult when it is smoldering and often defies all of the usual tests. If there are no clinical manifestations of rheumatic activity, *however*, it is assumed that rheumatic activity is either absent or so minimal as to be of little importance as regards the decision to operate.

Indications. In our opinion, tight mitral stenosis is *the* indication for mitral valvuloplasty. By tight is meant a valve area of 1.0 sq cm or less. This can usually be recognized accurately in patients with pure mitral stenosis without resorting to cardiac catheterization.

Mechanical narrowing of a mitral valve is well tolerated to a point. When it is but 20 *per cent of its* normal size, i.e., about 1.0 sq cm, symptoms are present at rest or on the slightest exertion (12, 22). We have encountered considerable difficulty in estimating larger valve sizes on clinical grounds alone, but have seldom had difficulty in recognizing "tight" mitral valves. In order to do this, aggravating factors must be eliminated such as thyrotoxicosis, pregnancy, active rheumatic carditis, subacute bacterial endocarditis, uncontrolled tachycardia, and other complicating episodes such as arterial or pulmonary embolism. In short, the patient is under good medical management without aggravating influences. The symptoms and signs derive from the mechanically obstructing mitral valve.

Nothing is so important as a careful history with one's attention focused on symptoms during the periods when these complicating events are *absent—a careful* physical examination, an x-ray and fluoroscopy of the heart, and an electrocardiogram. If the patient with pure mitral

toward, but not necessarily to, normal values early in the postoperative course.

Discussion

From these early postoperative observations, it is apparent that the surgical relief of mitral stenosis entails an evaluation not only of the stenotic valve itself, but also of mitral regurgitation, pressure and flow relations across the valve, arteriolar resistance in the lung, and right ventricular function.

The postoperative size of the mitral valve was increased in all cases but was only 30 to 50 per cent of the normal size. By the surgical technique used, it seems unlikely to this author that the size can be made greater As described in detail elsewhere (11), a valve area of 1.5 sq cm or more should result in restoration to almost normal activity, assuming a regression of pulmonary vascular changes and return of right ventricular function to normal. If the valve is 2.0 sq cm or more, the patient has symptoms only on excessive exertion. A certain and appreciable number of such patients may never progress to symptomatic disease (21). Surgery has certainly not been sufficiently perfected as yet to justify its use in patients with valve areas greater than 1 5 sq cm.

A general concept in the past has been that relief of stenosis must be at the expense of producing mitral regurgitation. Harken (2) was the first to recognize that it was possible to relieve stenosis without producing regurgitation. The data reported here amply confirm him in demonstrating that the valve orifice can often be increased to a size which enables the patient to live a life of all but truly excessive activity without the concomitant production of regurgitation.

The early as well as later return of pulmonary arteriolar resistance toward normal in some of our patients is extremely encouraging and indeed surprising because authoritative pathological opinion has been that this would probably not occur (14). Although relief of mitral valve obstruction would relieve pulmonary congestive symptoms, the patient might still remain relatively incapacitated if such elevated resistances persisted after operation.

The presence of auricular fibrillation in itself has no bearing on the decision to operate or not to operate. The incidence of embolism can

One of the pressing questions is whether the valve orifice will continue to remain patent for a prolonged period of time or whether it will become sealed off again in the course of weeks or months. Since the orifice is continually opening and closing, the only obvious ways in which it can become reduced in size again are by a recurrence of active rheumatic valvulitis or by thrombus formation on the fractured commissure at or shortly after operation, before endothelium has grown over the denuded areas. Sufficient objective data are as yet unavailable as regards the size of the mitral orifice six months or more after operation, but clinical follow-up on these patients indicates progressive improvement in their exercise tolerance over the course of the succeeding four to six months, which is possibly attributable to the regression of the secondary vascular changes in the lungs. After six months, their activity stabilizes and their capacity to exert themselves has shown no tendency to diminish. It would seem likely, then, that the valve orifice has remained unchanged in size for periods up to three years, which is the longest that any patients have been followed.

To date, 115 patients have had a finger fracture valvuloplasty performed by Dwight E. Harken. Sixty-five have been in his group 3 (23) (corresponding with certain modifications to the same grouping of the New York Heart Association). There have been four operative deaths, a 6 per cent mortality—all in the earlier part of the series. Among fifty patients in group 4, there have been eighteen operative deaths, a mortality of 36 per cent. With experience and with the development of suitable instruments, there have been no technical deaths in the last eighty or more operations. Arterial embolism has accounted for seven deaths, cardiac standstill, ventricular fibrillation, and shock have accounted for about ten deaths, and the remainder have been from miscellaneous causes. Much of this mortality occurred during the developmental period of this type of surgery. Details of the surgical technique and anesthesia will be found in the publications of Harken (16).

It is apparent that the operative risk is low in those patients who have pure mitral stenosis and who are incapacitated by exertional dyspnea, orthopnea, hemoptysis, and paroxysmal nocturnal dyspnea but whose hearts and livers are not greatly enlarged and who have little or no edema. In those who do have big hearts and signs of right ventricular failure, i.e., in those who are completely incapacitated, the risk is considerable,

stenosis has any four of the following eight manifestations, he can be confidently assumed to have a mitral valve area of 1 0 sq cm or less, i.e., a tight mitral stenosis (12).

1. Severe exertional dyspnea on one flight of stairs
2. Left auricle moderately or markedly enlarged by fluoroscopy
3. Pulmonary artery moderately or markedly enlarged by fluoroscopy
4. Right ventricular hypertrophy by electrocardiogram
5. Auricular fibrillation
6. Heart 20 per cent or more enlarged by roentgenogram
7. Hepatomegaly (4 cm or more below the costal margin)
8. Three to four plus edema

Four or more of these manifestations are, in our opinion, indications for mitral valvuloplasty.

The presence of mitral insufficiency or involvement of other valves in the rheumatic process complicates the decision regarding surgery. It must be remembered that mitral valvuloplasty is designed specifically for relief of severe mitral stenosis If other valves are involved, the degree of improvement from mitral valvuloplasty will not be so great as in pure mitral stenosis.

In patients with mitral stenosis, the estimation of the severity of other valve lesions is not easy In our experience, the best clue to the *severity* of *aortic insufficiency* is the diastolic blood pressure; of *aortic stenosis*, the duration of systole on a brachial arterial pressure tracing; of *mitral insufficiency* the presence of left ventricular hypertrophy, combined ventricular hypertrophy, or even the absence of right ventricular hypertrophy in a patient with both systolic and diastolic murmurs at the apex whose symptoms and signs would lead one to expect that right ventricular hypertrophy ought to be present; of *tricuspid insufficiency* an enlarged pulsating liver; and of *tricuspid stenosis*, pronounced edema and ascites and an elevated venous pressure not responding well to the usual forms of cardiac therapy. Cardiac catheterization is now reserved for those cases which remain doubtful using the usual clinical measures. If one or more valves other than the mitral have serious disease, it is not in the best interest of the patient to operate. If one or more valves are minimally involved and the mitral valve is severely stenosed, a good but not excellent result from successful mitral valvuloplasty may be anticipated.

Dr Dwight E. Harken has performed the surgery, with the able assistance of Drs. R E. Farrand, H. L. Black, and J. E. Dickson, III.

Without the collaboration and fundamental contributions to the pathological physiology and clinical and physiological correlations by Drs. R. Gorlin, B. M. Lewis, and F W. Haynes, this work would not have been possible.

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and the results are not so marked or so sure, but in some the benefit has been dramatic.

From this study, some of the problems of the effectiveness of mitral valvuloplasty have been answered, but many remain to be solved. The results are so encouraging, however, that this surgical approach seems to rest on solid ground.

Summary

1. The salient points of the pathological physiology and clinical manifestations of mitral stenosis and of surgical objectives have been discussed.

2. Twelve patients with mitral stenosis on whom valvuloplasty was performed by Dr. D. E. Harken at the Peter Bent Brigham Hospital have been studied before and two to six weeks after operation in order to obtain objective information regarding the effectiveness of the surgical procedure.

3. The orifice of the mitral valve was increased in size in each case, but in none was it brought back to normal. In the majority, the postoperative size was such that normal but not excessive activity should be and actually was regained.

4. Mitral regurgitation was not produced in eleven of these twelve cases.

5. The immediate effect of operation in ten of twelve cases was to lower the pressure in the pulmonary circuit rather than to increase cardiac output.

6. In two patients, there was a dramatic decrease and in two others a significant decrease of pulmonary arteriolar resistance shortly after operation. In two, this resistance had returned to practically normal values seven months after operation. Whether changes in the arterioles of the lung will regress completely with the passage of time in all cases cannot be answered as yet.

7. There was a general tendency for the diastolic filling pressure of the right ventricle to decrease postoperatively to or toward normal.

8. Operative indications and risks have been discussed.

The author is merely the spokesman for a team at the Peter Bent Brigham Hospital who have recently been concerned in the study of mitral stenosis.

Chapter 9

SURGERY OF ACQUIRED VALVULAR DISEASE *

Robert H. Wylie †

Introduction

A CONSIDERATION of the surgery of acquired valvular disease at this moment involves principally the surgery of mitral stenosis. However, the surgical correction of aortic stenosis and insufficiency of the mitral valve is on the horizon, but at this time there is not enough evidence at hand to evaluate these procedures. Just beyond the horizon also are other techniques of dealing with acquired lesions of the cardiac valves, but these will await the further development of methods for carrying on the circulation artificially in order that one may operate under direct vision in a bloodless field

History

At the beginning of this century the idea of surgically opening the stenosis of the mitral valve occurred to D W Samways (1) and Sir Lauder Brunton (2) The latter had made the observation that the stenotic mitral valve could be opened readily at the time of autopsy and suggested that such an opening should be made in the slits of the valve and not across the leaflets. Thus in 1902 he wrote, "On looking at the contracted mitral orifice in a severe case of this disease one is impressed by the hopelessness of ever finding a remedy which will enable the auricle to drive the blood in a sufficient stream through the small mitral orifice, and the wish unconsciously arises that one could divide the constriction as easily during life as one can after death. The risk which such an operation would entail would naturally make one shrink from it,

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function Thus the stenosis is relieved without producing regurgitation back through the valve.

There is no difference of opinion now among the surgeons who have had the greatest experience in this field that the use of the left auricular appendage as the avenue of approach to the mitral valve is far superior to any other technique. There is some question, however, as to the best method of separating the commissures of the stenotic mitral valve. Harken (13) is of the opinion that in most instances this separation can be adequately performed by finger manipulation which he calls finger fracture valvuloplasty He reserves the technique of incising in the commissures for a minority of the cases Blalock concurs with this practice On the other hand Bailey (14) and his associates use an incision in the commissures in the majority of their cases because they believe that the division in the commissures is better controlled by this method and there is less likelihood of tearing into the valve leaflets which has the disastrous effect of producing an uncontrollable regurgitation Also this group believes that a more adequate separation back to the normal tissues of the valve bases is made possible by an incision thus to ensure better valve function with less likelihood of the recurrence of the stenosis

Anatomy and Physiology of the Mitral Valve

For a complete understanding of the basic principles underlying these surgical maneuvers it is necessary to consider briefly the *anatomic*, pathologic, and physiologic aspects of the mitral valve. The normal mitral valve is a somewhat conical cuff of thin flexible membrane. The apex and outer surface of the apical half of this cuff are attached by the numerous guy wires of the chordae tendineae originating in the papillary muscles which arise from the ventricular wall. The chordae tendineae are grouped more heavily in two areas of the apex of the mitral cuff thus forming two components of the valve, the anteromedial and posterolateral leaflets The base of the posterior leaflet is attached at the atrioventricular ring The anterior or aortic leaflet is attached at its base to the ring surrounding the systemic aortic orifice and hence appears as a downward prolongation from the posterior border of the aortic orifice This anatomical arrangement is extremely important be-

but in some cases it might well be worthwhile for the patient to balance the risk of a shortened life against the certainty of a prolonged period of existence which could hardly be called life." It remained for Tuffier (3), however, to make the first attempt at surgical correction of an acquired valvular lesion. In 1914 he reported improvement in the condition of a patient having aortic stenosis after digital dilatation of the aortic valve by invagination of the wall of the ascending aorta. The previous year, after an unsuccessful attempt to open a congenital stenosis of the pulmonary valve by introducing an instrument through the wall of the right ventricle, Doyen (4) considered using the same approach for relieving the stenosis of the mitral valve

After this it was not until the 1920's that Cutler (5, 6) and his associates began an exhaustive experimental study of the problem. Their study led them to the surgical treatment of seven patients with mitral stenosis between the years of 1923–28. The approach to the problem was through the wall of the left ventricle using a valvulotome blindly—one of these patients survived. In 1923, Allen and Graham (7) attempted to relieve a stenosis of the mitral valve by means of a cardioscope which afforded some degree of visualization of intracardiac structures. In 1925 Pribram (8) in Germany using the technique of Cutler operated unsuccessfully upon a case of mitral stenosis. It is extremely interesting that Souttar (9) in England in the same year, using an approach through the auricular appendage, introduced his finger through the mitral valve successfully. This initial success, however, was not followed up and for the next eighteen years no further attempts were made Of these twelve operations for mitral stenosis in this early period only three patients survived.

The renewed interest and present state of our knowledge of the surgery of acquired valvular disease is the result of the pioneering work of Bailey (10), Harken (11), and Smithy (12) The older methods of attack upon the mitral valve had relied for the most part upon excising or incising the stenotic valve to produce some degree of regurgitation through the valve as the cost of relieving the stenosis. Bailey's conception, which he has carried into practice, has been to incise the valve between the leaflets in the commissures to more normal tissue at the base of the valve to widely open the stenotic valve while preserving its

recumbent on the right side. The chest wall is opened widely in the fourth interspace by an intercostal incision extending posteriorly from the transverse processes of the vertebrae to the lateral border of the sternum anteriorly A small incision is made in the pericardium and 5 cc of 5 per cent Novacain are instilled and allowed to remain in the pericardial sac for five minutes with the incision clamped. The pericardium is then incised longitudinally 1 cm anterior or posterior to the phrenic nerve depending upon the position of the underlying left auricular appendage The left auricular appendage usually is distended and easily accessible In four instances, however, the appendage has been the site of an organizing or organized thrombus. In two instances the auricular appendage thus involved appeared as a rudimentary process about the size of the tip of the index finger After infiltration of the base of the auricular appendage with ½ per cent Novocain, a purse string suture of #1 braided silk is passed about the appendage at its base. A noncrushing clamp is closed over the base of the appendage, and a portion of its tip is amputated The right index finger is inserted in the left auricle as the clamp is released and the purse string suture drawn snugly about the finger. In the instances where the auricular appendage is rudimentary and obliterated, a modification of this technique entails passing the purse string suture about the appendage in the adjacent auricular wall and incising down within the wall of the obliterated appendage to gain access to the auricle When the Bailey type knife is introduced with the finger, two gloves are worn on the operator's right hand The blade of the commissurotomy guillotine knife is inserted between the gloves on the index finger—the tip of the outer glove having been removed and an opening made at the base of the index finger.

The finger is well tolerated in the auricle, and exploration is carried out to find the mitral orifice The size of the orifice is determined, and an attempt is made to ascertain the site of the commissures It is important to note at this time the presence or absence of a regurgitant jet coming back through the valve and to determine the extent of fibrosis and calcification involving the valve leaflets—particularly the anteromedial leaflet If the disease has not involved this anterior leaflet it will be felt to bulge forcibly against the finger with each systole

The finger is then forcibly introduced through the stenotic mitral orifice with pressure exerted in the direction of the anterolateral com-

cause the large anterior leaflet is demonstrated as a baffle covering the mitral orifice and deflecting the flow of blood in systole through the aortic opening. Thus the large anterior leaflet is the main structure in protecting against marked regurgitation through the mitral valve, and any interference with this function as a baffle against the aortic flow by operative tear or by disease will lead to compromising regurgitation.

The small posterior leaflet of the valve is of secondary importance in the function of the mitral valve. Lying as it does along the lateral wall of the ventricle it is out of the line of the aortic thrust of blood in systole, but also because of this position it is displaced inward by the contraction of the ventricle thus permitting its leaflet to purse with the anterior leaflet to affect efficient closure of the valve.

The portions of the conical cuff which lie between the ends of the valves become infolded in the closure of the valves, and it is these areas of infolding which become fixed in disease to produce an anatomic reality—the commissures.

In rheumatic disease with the fibrosis and contracture dependent upon it, the mitral valve becomes distorted. This distortion may be limited in extent and may resemble merely a purse string puckering of the valve orifice with the main portions of the leaflets remaining soft and pliable. In this instance where the valve orifice only is involved it is conceivable that the valve leaflets may close above the rigid stenotic opening to prohibit regurgitation. In other instances the disease involves greater portions of the cuff leaving a flexible margin only along its base. In far-advanced disease the whole valve becomes a rigid, inflexible, and often calcified plaque with a small ovoid fish mouth opening. In some of these latter instances where the valve leaflets are extensively involved and shortened, mitral regurgitation may be the predominating feature and surgical interference by manipulation of the valve is not indicated.

Surgical Technique

The technique of operation which has been employed on the First Surgical Division at Bellevue Hospital where Himmelstein, Lambert, and the author have worked as a surgical team on this problem is fashioned closely after the techniques of Bailey and Harken from both of which it differs, but little.

The operation consists in a left lateral approach with the patient lying

digitalized patient has been required as one criterion of acceptance of patients for commissurotomy.

Patients who give evidence of active rheumatic infection or, of course, subacute bacterial endocarditis are not acceptable for operation. Also the presence of any major involvement of any of the other valves of the heart is at present a definite contraindication Patients with a small degree of mitral regurgitation as evidenced by a systolic murmur have been considered for operation only where there was no evidence of left ventricular hypertrophy. Also minor aortic diastolic murmurs in the absence of other clinical evidence to support aortic insufficiency have not been considered contraindications. Patients with a small degree of mitral regurgitation as evidenced by a systolic murmur have been considered for operation only where there was no evidence of left ventricular hypertrophy Also minor aortic diastolic murmurs in the absence of other clinical evidence to support aortic insufficiency have not been considered contraindications Bouts of frank cardiac failure have not been regarded as a deterrent to operation as long as the patient is compensated at the time of the procedure Auricular fibrillation is not considered as of significance in the decision to operate

It is our philosophy at the present time that it is more reasonable to accept the severely incapacitated patient for surgery where there is little doubt as to the progressive and crippling nature of the lesion than it is to accept those whose incapacity is only indicated in the future. This philosophy naturally carries with it a higher mortality as the more severe cases are encountered, but at the present time the follow-up is not long enough to advocate the operation in those patients who are not definitely incapacitated or fail to show evidence of a definite degree of physiologic block as determined by cardiac catheterization studies. This attitude may be altered with the passage of time when more adequate follow-up will be available.

Results

A consideration of the results of this procedure should be focused first upon the immediate operative results in terms of mortality, second upon the early postoperative results in terms of a return to normal clinical activity with evidence of relief of the physiologic block at the mitral valve, and third upon the long-term follow-up where the problems of

missure. In most instances the valve splits in the region of the commissures after the initial resistance of the fibrous ring at the mitral orifice. It has been our experience in a limited group that the values in about one-third of the cases do not open widely by this method. In those instances, first where the valve cone is greatly elongated with a rubbery aperture and second where there is extensive fibrosis and calcification well back on the bases of the valve, one initial attempt is made to dilate, but if this fails the knife is employed. The knife is then protruded through the opening, and the hooked blade engaged in the anterolateral commissure. Approximation of the guillotine is carried out to divide the commissure. It has not seemed necessary in any of our cases to employ the knife in division of the posteromedial commissure.

The finger and knife are now withdrawn from the auricle as the purse string is tied. The cut edges of the auricular appendage are oversewn to ensure closure. Several sutures are placed in the pericardial opening, but no attempt at real closure is made The chest is closed with intercostal tube drainage.

Selection of Patients for Operation

In the selection of cases for operation we have relied heavily as surgeons upon the judgment of our medical confreres Drs. Richards, Cournand, Ferrer, and Harvey. I wish to emphasize here the value of close cooperation of a medical and surgical team in the selection and aftercare of these patients. It is obvious that all cases with stenosis of the mitral valve are not candidates for this operation. As experience accumulates, follow-ups on our patients become more adequate and the risk of operation in different groups better established, these indications will undoubtedly change.

At the present time, the group at Bellevue Hospital is of the opinion that the following are indications for a direct attack upon the stenotic mitral valve. Clinically, there should be symptoms and signs of pulmonary engorgement, dyspnea and cough on exertion, paroxysmal dyspnea, pulmonary edema, or hemoptysis In addition, supportive evidence of pulmonary hypertension and diminished output of blood from the left ventricle as a result of the block at the mitral valve is sought through cardiac catheterization studies in the digitalized patient. Elevated pressure in the pulmonary artery with a diminished cardiac output in the

catheterization studies one year following surgery. These studies now add the weight of laboratory evidence to that of the clinical, and also show that there seems to be continuous improvement in these patients. The status at one year following operation is better than at one month after surgery from the evidence of these data.

Of the two patients who are considered improved symptomatically at this time, one we believe will prove to be our poorest result. There was a mild degree of regurgitation through a stenosed calcified mitral valve in this case. The degree of regurgitation was not lessened by incising the commissure anteriorly to relieve the stenosis, because of the immobility of the leaflets Also the histologic examination of the auricular appendage showed active rheumatic auriculitis in spite of no evidence of clinical activity during a long period of observation prior to operation. Although auriculitis has been found in three other of our patients we believe that it is significant in this case because of a prolonged febrile course post-operatively Thus, in the early follow-up, rheumatic activity, although unsuspected clinically, is actually shown to be present in some of these patients and may act as a limiting factor

Another factor which may alter the result obtained from mitral commissurotomy is the secondary obstruction in the pulmonary circuit due to pulmonary atherosclerosis in long-standing cases of mitral stenosis. Julian Johnson (17) has drawn attention to this and believes that the obstruction due to pulmonary vascular lesions in some cases may be significant enough to negate the effect of surgical opening of the mitral valve. Our group is investigating this aspect of the problem but as yet has no evidence of a convincing nature.

A complication has occurred in two of our patients during the period of six weeks to four months following operation This has consisted in recurring attacks of fever and bilateral chest pain without cough lasting from five days to a week The explanation of these episodes is not clear at the present time. With them there has been no evidence of cardiac decompensation although in one case auricular fibrillation was present transiently It is surmised that these attacks may represent rheumatic activity, possibly a pericarditis. However there has been no evidence either by x-ray or by electrocardiography to substantiate that diagnosis.

As has been suggested in this review of the early follow-up in a small group of patients there are a number of factors such as the effect of con-

secondary contraction of the stenotic mitral valve and the effects of continued rheumatic activity will be answered.

A full evaluation of this procedure cannot be given until the answers to these last problems are known. In the meantime, the evidence at hand indicates that the mortality of the operation and the early results in properly selected cases certainly justify the continued use of this operation. Whereas the initial mortality reported on the first small groups of patients operated upon by Harken and Bailey was 60 per cent, the development of technique and better selection of patients has brought the mortality down to nearer 10 per cent in these experienced hands. Alfred Blalock (15) has recently reported two deaths in a series of twenty-five cases. In one of the patients that died, intracardiac manipulation was not performed because of the obliteration of the auricular appendage and death was due to cerebral embolism Naturally the mortality will fluctuate with the severity of the disease, but where selection of the patients has been strict the chance of improvement at present well justifies the risk.

What are the early results and what are some of the limitations that are recognized? At the present time there is little statistical evidence even on the early results in these patients. Glover (16) has reported for Bailey's group on 41 patients on whom commissurotomy was performed. Twenty of these or approximately 50 per cent are considered to be excellent results from the clinical standpoint. The remainder, or 21, they consider to be improved. In this respect our experience, although small, is worth reciting. Nine patients between the ages of twenty-six and forty-nine years have been accepted for this operation, and seven have survived. One of these patients died at operation when the posterior wall of the auricle ruptured as the finger was being introduced through the auricular appendage. The other had a cardiac arrest during intracardiac manipulation and although normal rhythm was re-established by cardiac massage, the patient did not regain consciousness and died eighteen hours later.

The status of the seven survivors is as follows: five of these patients are, from a symptomatic point of view, considered as excellent early results and two are classified as improved at the present time. Of the five patients who are considered to be in the excellent category, two who were operated upon nineteen and sixteen months ago have had cardiac

been somewhat encouraging, it is highly improbable that such grafts would flourish in the scarred areas of diseased valves.

The third line of endeavor in the correction of the insufficiency of the mitral valve has been directed toward the use of pedicled flaps placed across the left ventricle just below the mitral valve so that the flap will obstruct the incompetent valve in systole Gordon Murray (22) has used vein segments while Bailey has employed pericardial grafts to achieve the same purpose. It is impossible at this time to give a proper evaluation of this method. It is fair to say that the problem of insufficiency of the valves of the heart is going to be a difficult one to solve because of the complicated mechanism of the valve function.

Aortic Stenosis

Aortic stenosis is another acquired valvular lesion which is challenging the ingenuity of investigators in this field It is extremely interesting to recall that the first successful operation for an acquired valvular lesion was performed in 1914 by Tuffier (3) As has been noted previously he was able to invaginate the wall of the ascending aorta through the stenosed aortic opening using his finger and apparently to widen the stenotic area as the patient was living ten years later Investigation of the possibility of treating this lesion surgically was revived by the late Horace Smithy (12) in the 1940's. Incision of the stenotic aortic valve using the left ventricular approach has been performed by Blalock and by Bailey but without success The problem of opening the stenotic aortic valve is not only complicated by the difficulty of approach, but also the production of appreciable degree of regurgitation is not tolerated.

More recently Bailey and his associates have attempted to stretch the stenotic aortic valve using a dilator instead of an instrument to incise the valve, with more success Originally an approach was made through the carotid artery and down the aorta, but apparently this route has now been abandoned in favor of the ventricular approach It is only possible now to indicate the methods that are being employed to attack the complicated problems involved in the solution of insufficiency of the mitral valve and of stenosis of the aortic valve It is probable that even now there are other methods under investigation which will solve these complicated surgical problems. On the other hand it may be that the solutions will not be found until operations can be performed in a dry field

tinued rheumatic activity and pulmonary arteriosclerotic changes which will have to await a longer close follow-up for a proper evaluation. Subsequent observations also may show that there is a gradual re-formation of the stenosis either with or without recurring rheumatic activity. However, the early results that are being obtained in the treatment of mitral stenosis by a direct attack on the valve are good, and we believe they far outweigh the risk of the operation in carefully selected patients

Pulmonary Edema in Mitral Stenosis

In addition to the method of treating mitral stenosis by direct attack upon the valve, efforts have been made to prevent the bouts of pulmonary edema which occur in this disease. Attempts to solve this problem have been made by the anastomosis of systemic and pulmonary veins as performed by Sweet (18). Harken (19) also has suggested the making of an interauricular defect to alleviate bouts of pulmonary edema. The utility of any such shunting procedures must be limited. In a well-marked mitral stenosis there is a diminished outflow of blood from the left ventricle and there is an inability to increase this output with exercise. Therefore any decrease in the amount of blood reaching the left ventricle, as might occur in the production of a shunt, will not be tolerated. It seems clear now that any indirect surgical attack on the problem of *mitral stenosis is inferior to that of removing the crucial* block in the circulation by surgical opening of the stenotic area itself.

Mitral Insufficiency

The surgical correction of insufficiency of the mitral valve is distinctly in the experimental stage of development. Investigation of this problem has been directed in the main along three lines. First, ingenious mechanical plastic valves have been anchored in place in experimental animals. It is certainly possible that such mechanical valves could be introduced and secured in the diseased valves of humans by the same techniques, but it is very doubtful that these valves would continue to function for any extended period of time.

Second, efforts have been made to repair experimental defects in valves using tissue grafts. Gordon Murray (20) used inverted segments of vein, and Templeton and Gibbon (21) vein and pericardial grafts to accomplish this feat in animals. Although the fate of these grafts has

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under direct vision—which means the perfection of a technique of extracorporal circulation.

At this time in the midstream of progress in the field of acquired valvular surgery it is possible to state that the operation for mitral stenosis is of great benefit to a selected group of patients with this disease. The future with an adequate follow-up of these cases will prove whether these patients are permanently cured or whether they have been given worthwhile respite from the continued ravages of rheumatic disease.

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Chapter 10

SURGICAL REVISION IN CONGENITAL CARDIOVASCULAR DISEASE*

George H. Humphreys II†

OF ALL of the physiologic systems which in later life are so intricately interwoven to form the complete organism, the cardiovascular system is the earliest to become functionally differentiated in the embryo. Unlike the nervous, skeletal, digestive, or urogenital systems, it becomes functional almost as soon as it forms, and on its continued and uninterrupted function life itself depends. From the time, approximately 14 days after fertilization, before which the developing ovum depends on simple osmosis for its metabolic exchange, until the revolutionary physiologic changes which follow birth and independent life, first the chorion and then the placenta carry on by means of the circulatory system the activities of digestive system, kidney, and lung while these organs develop without function. In order to be able to carry on this vital role so early in embryonic life, it is evident that the tissues of the circulatory system cannot be highly specialized. It is not surprising therefore that these tissues retain much of their primitive vigor throughout life until eventually their degeneration becomes synonymous with senescence itself.

The circulatory system goes through a complicated evolution, which not only reproduces in anatomic pattern a phylogeny of almost inconceivably remote antiquity but which also is subject to arrests or aberrations in development at almost every stage. The resultant abnormalities, if not of such an extent that fetal life cannot continue, are termed, after birth, congenital anomalies, or they are given the misnomer of congenital heart disease. It is important, especially from the surgeon's viewpoint,

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to remember that disease in the sense of a noxious or destructive agent attacking normal tissue is not present. The tissues are normal; they are simply arranged in an abnormally atavistic or bizzarre anatomical pattern which interferes more or less seriously with normal function. It is this fact which renders these conditions peculiarly amenable to surgical correction if suitable techniques can be devised to rearrange the pattern to one which is nearly or quite normal, or, failing that, to one which permits more nearly normal physiologic function.

It is not the purpose of this presentation to discuss the manifold aberrations in development of peripheral vessels. Most of these are of little clinical importance except for large or multiple abnormal arteriovenous communications, and they are usually, if it is possible, best treated by simple removal. In this field there is little that is not well known and less that is new But recently great advances have followed development of surgical and anesthetic techniques which permit more or less lengthy and meticulously careful surgical manipulations within the thorax. In this region the surgeon can now approach directly and at leisure anomalies of the major vessels and, within expanding limits, anomalies of the heart itself.

It has been customary to classify the more frequent of these anomalies in a descriptive way, labeling them with the names of those who first called attention to a particular pattern, or by the pathologic term of the most conspicuous anomaly and pigeonholing them *in no coherent order*. But as we become more familiar with the great variation in pattern seen *in the operating* or autopsy room, these arbitrary categories tend to break up into numerous subdivisions which merge into each other or combine in multiple variations which defy rigid classification Yet some order must be achieved if we are to discuss them in practical terms and especially if we are to approach them in a way which will permit us to separate out those which can be revised from those which cannot. This is even more necessary if new answers are to be found to previously unanswered problems.

A logical approach can perhaps be made by first separating out those anomalies which merely represent persistence into postnatal life of a vascular or intracardiac pattern which is normal at some stage before birth These anomalies represent failures in normal involution (Table III)

The next group might include those anomalies which result from the abnormal involution of structures which normally persist, or combinations of these with persistence of structures which normally involute (Table IV). Finally, there is a group in which the course of development is abnormal from the beginning. These do not represent any stage

TABLE III

Persistence of Normal Fetal Anatomy
(Failure of Normal Involution or Development)

A Patent ductus arteriosus
B Patent foramen ovale
C. Persistent left superior vena cava (entering coronary sinus)
D. Double aortic arch
E. Patent interatrial foramen (auricular septal defect)
F. Ventricular septal defect
G. Persistent truncus arteriosus
H Common ventricle (pre-reptilian heart)

TABLE IV

Involution of Structures Which Normally Persist, Alone or Associated with Persistence of Structures Which Normally Involute

A. Coarctation of aorta
B Right aortic arch and associated anomalies
C. Right subclavian originating from descending aorta
D. Right-sided or bilateral ductus arteriosus
E Valvular stenosis
  1. Tricuspid Rudimentary right ventricle, pulmonary atresia, auricular septal defect
  2. Pulmonary "Pure," with patent foramen ovale
  3. Mitral with auricular septal defect—Lutembacher's syndrome
  4 Aortic Subaortic stenosis
F. Infundibular stenosis with failure of closure of ventricular membranous septum—tetralogy of Fallot
G. Atresia of pulmonary artery with failure of closure of ventricular membranous septum

through which the fetus normally passes, but the stage of fetal development at which they originate can still be determined through knowledge of the time relationships of normal development (Table V). It should be emphasized that combinations of all three groups are frequent. Indeed, the presence of an anomaly of the third group, most of which originate very early in fetal life, may be a factor in altering the normal development pattern of other structures later on.

If we now arrange these groups in parallel columns and list them in approximate chronological order in terms of fetal development, certain obvious generalizations immediately become apparent. These may be helpful not only in bringing the jumble of apparently arbitrarily defined yet overlapping anomalies into a comprehensible order, but also in understanding the fundamental relationships of the various conditions to the possibilities for their correction (Table VI). It immediately becomes evident, for example, that the later is the stage in fetal development which the anomaly represents, the better is the prognosis. Anomalies representing failure of involution of structures normally present in a 10 or 12 mm embryo are for the most part correctable by surgery (for example, patent ductus and double aortic arch) or they cause little physiologic disturbance (patent *foramen ovale*). In the second group, likewise, anomalies caused by involution of structures which usually persist combined with persistence of structures which usually involute, if their origin does not go back of the 12 *mm embryo*, either cause no symptoms (right aortic arch) or they can be completely corrected by operation (coarctation of the aorta).

TABLE V

Abnormalities of Development

A. Pulmonary vascular anomalies
   1. Aberrant arteries from aorta
   2. Pulmonary veins entering vena cava or right atrium
   3. Vena cava entering pulmonary vein or left atrium
B. Abnormal origin of tricuspid leaflets with interatrial defect (Ebstein's complex)
C. Overriding aorta without transposition (Eisenmenger's complex)
D. Transposition of great vessels (with associated anomalies)
E. Dextrocardia (dextrorotation or situs inversus with levorotation)

If, however, there are anomalies originating at an earlier stage, the problem becomes more difficult. Correction of stenosis of the pulmonary valve can now be at least partially achieved by the procedure devised by Brock, but no sure way has yet been found to overcome congenital stenoses of the other valves and the anomalies usually associated with them. The immediate brilliant results obtained in tetralogy of Fallot by creation of an artificial ductus are achieved by introducing a compensating abnormality which in many cases creates a more nearly normal

The next group might include those anomalies which result from the abnormal involution of structures which normally persist, or combinations of these with persistence of structures which normally involute (Table IV). Finally, there is a group in which the course of development is abnormal from the beginning. These do not represent any stage

TABLE III

Persistence of Normal Fetal Anatomy
(Failure of Normal Involution or Development)

A. Patent ductus arteriosus
B. Patent foramen ovale
C Persistent left superior vena cava (entering coronary sinus)
D Double aortic arch
E. Patent interatrial foramen (auricular septal defect)
F. *Ventricular septal defect*
G. Persistent truncus arteriosus
H Common ventricle (pre-reptilian heart)

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physiologic function without correcting the anomaly itself. It is not yet certain whether this balanced abnormality can be maintained indefinitely. Abnormalities which originate earlier than the 7 mm embryo, in which nearly all of the third group fall, have as yet not been substantially helped by operation.

It is also apparent that those lesions which produce deep and constant cyanosis for the most part originate very early and cannot be corrected,

TABLE VI

Fetal Age	*Group I*	*Group II*	*Group III*	
Term	Ductus arteriosus Foramen ovale Left vena cava Double aortic arch	Coarctation Right aortic arch Right subclavian from descending aorta Right or bilateral ductus		Correctable or harmless
12 mm	Interatrial foramen * Membranous septal defect †	Valvular stenoses † Infundibular stenosis *	P V.A *	Partially correctable
7 mm	Interventricular foramen * Truncus arteriosus ‡ Common ventricle ‡	Atresia of pulmonary artery ‡	Ebstein's * Eisenmenger's ‡ Transposition ‡ Dextrocardia ‡	Not correctable

* Cyanosis inconstant.
† Cyanosis variable or late in appearing
‡ Cyanosis constant and deep.

while those in which cyanosis is variable, inconstant, or late in appearing are related to anomalies of a later developmental stage, in some of which spectacular physiologic improvement can be obtained by operation even though a normal anatomic pattern is not restored. It is this group in which further advances seem most likely to be made.

Let us review, then, briefly the present status of surgical revision of these anomalies.

Persistent patency of the ductus arteriosus heads the list. It is a condition

which is normal at birth, and becomes abnormal only when postnatal involution fails to occur. It is also the first of all of these anomalies to have been successfully corrected, and it is now the anomaly in which complete restitution to normal is accomplished with least risk. The *symptoms* which result from persistent patency of the ductus arteriosus vary with the size of the opening. When it is small they may be negligible, at least in childhood and youth, but when the opening is large, allowing correspondingly large abnormal flow of blood from the aorta back into the pulmonary artery, the effects on health may be profound. Yet even in the apparently symptomless individual unexpected improvement often follows closure of the ductus, and it seems probable that life expectancy is prolonged

The diagnosis is usually not difficult, for in the great majority of cases after infancy a characteristic machinerylike murmur is readily heard over the pulmonary area Those cases in which the murmur is unusual are usually instances in which the ductus is very large and the abnormally high pressure in the pulmonary arteries has resulted in sclerosis and in a reduction in diastolic flow through the ductus, or even a reversal of flow In such cases the diagnosis can be made from history, roentgenographic and electrocardiographic findings, or, if necessary, by catheterization of the right heart and pulmonary artery.

Whether the ductus should be closed by division of the vessel and suture of the cut ends, or by simple double ligation *in continuity is still* a matter of discussion Division and suture is probably a more certain method of ensuring permanent closure, but carries a somewhat higher risk It is rare for a new channel to form when double ligation is properly carried out, and the risk of this procedure in competent hands is very slight In the presence of late complications, however, the risk is much increased Associated subacute endarteritis, though curable by operation alone, is usually more safely handled by control of the infection with antibiotic treatment, followed by closure of the ductus after the patient has been restored to comparative health When myocardial failure or reversal of flow has supervened, the risk is high, yet the prognosis in such cases is usually so poor that the attempt must be made. Thus it is now generally agreed that operation is indicated in practically all cases of patent ductus arteriosus.

Coarctation of the aorta is the next anomaly to yield to surgical correc-

tion. It represents a relatively minor deviation from the normal pattern of involution, and complete restitution to normal can usually be accomplished. Like persistent patency of the ductus arteriosus its effects vary with the severity of the lesion. When the aorta is completely closed, the resulting hypertension above the closure and decreased ability of the circulation below to meet sudden or heavy demands will become apparent early in life. Mild constrictions, on the other hand, may cause no obvious symptoms, and often escape detection until late complications develop.

Here again the diagnosis is readily made if the condition is suspected. Increased arterial pressure in the arm, contrasted with absent pulse or diminished pressure in the legs, is characteristic. A systolic murmur is usually present, but it may be inconspicuous and is usually of little diagnostic help. Characteristic notching of the ribs by the enlarged and tortuous intercostal collaterals is often seen on chest roentgenograms but is not always present, especially in children. Special diagnostic techniques are usually not necessary. Ballistocardiographic tracings show a characteristic abnormality in the pulse wave pattern and are useful not only in judging the severity of the lesion but also in evaluating the effectiveness of operative relief Retrograde angiograms not only confirm the diagnosis but localize the lesion and give an indication of its extent.

The risk of operation, involving excision of the coarcted segment and end-to-end anastomosis of the aorta, is a real one but in competent hands it is steadily diminishing After childhood, degenerative changes in the vessel wall add to technical difficulties, increasing the risk. In such cases alternate procedures may be necessary such as the use of the enlarged left subclavian or an aortic graft to bridge a gap, measures in which the ultimate outcome is still uncertain, although the immediate results are promising. There is some question as to whether a coarctation, corrected in early childhood, may recur due to failure of the anastomosis to grow with the growing aorta Experimental evidence now indicates that this fear is unfounded if continuous sutures of nonabsorbable material are avoided

As in the case of patent ductus, it seems probable that individuals with coarctation of the aorta, even when there are no apparent symptoms, suffer a subtle handicap which increases with the years and often

leads to premature death through complications in middle age. Since the risk of operation is not great in childhood, but increases rapidly after maturity, it is to be hoped that the condition will in the future be recognized early and operative correction carried out even in the absence of symptoms

Anomalies of the aortic arch, in contrast to the previous abnormalities, cannot be surgically restored to a normal anatomic pattern They occur rarely, and many are of little clinical interest since they cause no real disturbance in circulation When symptoms do occur, it is usually because pressure or constriction of other organs is caused by the presence of anomalous arteries. Variations are so great that it may almost be said that no two situations are identical, yet certain patterns associated with recognizable symptoms and signs are sufficiently frequent to merit discussion, especially since operative relief is often possible.

Double aortic arch, a simple persistence of a normal fetal stage, results from failure of the right arch to involute between the subclavian and the point of juncture of the two primitive descending aortae. If this point remains sufficiently distal to the arches, no symptoms will result, and the condition will be discovered unexpectedly at autopsy or operation. It may also be recognized on roentgenograms. If, however, the arches join high, a rigid vascular ring is formed about the trachea and esophagus which interferes more or less seriously with breathing, swallowing, or both.

Usually symptoms develop early in infancy. A more or less constant stridor, worse during upper respiratory infections or with vigorous breathing, as in crying, should raise the question. Cyanotic attacks during feeding are also common, due to the fact that the esophagus can be distended only by pushing forward the membranous portion of the trachea Occasionally real esophageal obstruction is also a problem, especially with solid foods which pass only with difficulty through the angulated esophagus

The diagnosis can sometimes be made by recognition of compression or angulation of the tracheal air column on a lateral roentgenogram. Usually demonstration of the deformity is more apparent if the trachea is outlined by iodized oil Similarly a barium swallow will show characteristic forward angulation and usually a lateral distortion of the esophagus. If necessary, a more accurate demonstration of the exact pattern

of the vessels can be obtained by retrograde angiography, but this is a procedure of some technical difficulty in a small infant and not without risk if the patient is in poor condition, as is often the case.

Other aortic arch anomalies may also result in a vascular ring around the trachea and esophagus. Usually the primary disturbance is persistence of the right aortic arch, with abnormal involution of the left. The latter may remain as a fibrous cord joining a left innominate to the descending aorta. In other cases the ligamentum arteriosum may complete the ring by entering the descending aorta as it crosses behind the esophagus. The ring so formed is looser than that due to double arch because the pressure in the pulmonary artery is less and the vessel in consequence is softer. But if the ductus remains patent, aortic pressure is transmitted through it to the pulmonary artery and real obstruction results.

Distortion of the esophagus is also caused by anomalies which do not form a true vascular ring, and, occasionally, these are of sufficient degree to cause serious dysphagia. Simple persistence of the right aortic arch with involution of the left, though it causes a characteristic slight distortion of the esophagus, does not by itself have any clinical significance. The most frequent of these anomalies to cause symptoms is due to involution of the segment of right arch between carotid and subclavian with persistence of the segment from subclavian to the point of aortic junction This results in a long vessel originating from the descending aorta, passing behind the esophagus, and ending as the right subclavian. Another is due to an abrupt crossing over behind the esophagus of a persistent right arch associated with a normally placed descending aorta. Variations in this group are the rule, and exact anatomical diagnosis may not be possible before operation

In correcting the effects of these anomalies the surgeon must be guided by knowledge of the embryologic possibilities, and take care to release the trachea and esophagus by dividing the ring in such a way that no vital vessel is disturbed. In the case of a double arch the left arch can usually be cut between left carotid and left subclavian, though sometimes it is more expedient to divide it below the subclavian. It is necessary to select carefully the arch to be divided since not infrequently it may be found that a coarctation exists in one of them Either subclavian may be sacrificed. If the ring is due to a ligamentum arteriosum or patent ductus, division of this structure will suffice. Often the aper-

ture can be widened by pulling the vessel which crosses the front of the trachea forward and attaching it to the sternum, but since this is usually the base of the left carotid, it is dangerous to resect it. Indications for operation depend upon the severity of the symptoms and early recognition of the condition, before the infant's condition has become critical and while the risk is not high. Too often, however, the condition is not appreciated until after numerous episodes of pneumonia have added greatly to the risk.

Anomalies of the pulmonary vessels are rare lesions in which no single pattern stands out as a clinical syndrome. Pulmonary arteries arising from the aorta or other systemic vessels have been described in great variety Usually they are isolated anomalies associated with abnormal lung lobes and do not cause physiologic disturbance of the circulation though they may be associated with pulmonary anomalies requiring resection Occasionally, systemic veins may enter the pulmonary system, especially a persistent left vena cava. They usually cause little disturbance When they are found incidentally in the course of operation for other anomalies, they can be divided in most instances without hesitation

When one or more of the pulmonary veins enters one of the venae cavae or right atrium, however, the resultant overloading of the right heart may be serious unless there is a large interatrial septal defect. Although theoretically an ideal correction would be a reimplantation of the anomalous vein into the left auricle, this is rarely feasible technically. Blalock has recommended creation of a large communication between the auricles for this situation If only a single vein is involved, removal of the corresponding lobe, or even an entire lung, may be justified

Intracardiac anomalies as a group pose quite a different problem from those of the great vessels Arising from arrests or abnormalities at an earlier stage of fetal development, they also less often occur as single lesions In addition, the necessity of manipulating a sensitive and active organ without seriously interfering with its constant function still sharply limits the possibilities of successful surgery

Septal defects, especially those in the auricular septum due to persistent patency of the interatrial foramen, the effect of which may often ultimately be severe, seem to be the most likely of the intracardiac lesions of the first group to be correctable. Much interesting experi-

mental work is in progress, but as yet no method has been perfected which has been accepted as clinically useful.

Pulmonary stenosis, a term broadly used for a variety of lesions primarily of the second group, has been approached surgically with more success. In general, these conditions have in common combinations of anomalies which, on the one hand, restrict the flow of venous blood from the right heart to the lungs, and, on the other, divert a greater or less amount from the right heart into the left and so into the arterial tree As a result cyanosis is usually present.

Pure pulmonary stenosis may occur as a single lesion due to fusion of the cusps of the pulmonary valve without any other anomaly. Such patients are not cyanotic at rest since all blood entering the right heart chambers must leave through the narrowed pulmonary channel The result is an enormous increase in work load of the right ventricle which it meets by marked hypertrophy and development of a very high ventricular pressure. Even so the right heart frequently is unable to meet the demands of normal exertion with resultant dyspnea and rise in venous pressure. The latter, though distention of smaller venous channels, may produce transient cyanosis of venous origin, but arterial unsaturation does not occur, and dyspnea is due to hypercapnia rather than to anoxia.

More often, when the pulmonary valve cusps are fused, there is from birth sufficient back pressure in the right atrium to hold the foramen ovale open, and to permit, especially during exertion, decompression of the right heart by shunting part of the venous return into the left. Cyanosis of arterial unsaturation therefore results. Although this situation is also termed "pure" by Taussig in order to distinguish it from the more complex forms of pulmonary stenosis, it is not a single lesion.

These two forms of "pure" pulmonary stenosis have much in common, being distinguished clinically only by the presence or absence of arterial unsaturation Both result in loud harsh systolic murmurs in the pulmonary region with absence of the second sound. Cardiac enlargement varies from almost none to very great in advanced cases, but evidence of right ventricular hypertrophy is always present on electrocardiogram and usually on roentgenographic silhouette. The latter also frequently demonstrates a dilated pulmonary artery shadow at the base of the heart in contrast to diminished vascular markings in the lung fields.

This feature helps distinguish this from the pulmonary stenoses of earlier developmental origin in which the arterial shadow is usually small or absent. Catheterization shows an increased right ventricular pressure in proportion to the degree of stenosis, and a much damped pressure in the pulmonary artery if the catheter can find its way through the valvular orifice. The "purity" of the anomaly is proved if pressure is higher than that in the systemic arteries and if saturation in the outflow tract is the same as in the atrium.

Brilliant results are now obtainable in pure pulmonary stenosis by Brock's method of dividing the fused valve and stretching it with sounds. This procedure does not completely restore normal anatomy since the valve is still abnormal, as demonstrated by persistence of the murmur. But that nearly normal valvular function and pressure relationships can be achieved is shown by postoperative catheterization studies. Thus a seriously disabling anomaly is converted to one of minor consequence. If a patent foramen ovale is also present, this anomaly is, of course, not changed, but the altered pressure relationships convert the flow through it from predominantly right to left to the reverse, thus eliminating cyanosis

The risk of pulmonary valvulotomy may be high if the patient is close to right heart failure In an early, well-compensated case the operation is usually well borne in spite of the fact that it involves passing a succession of instruments through the right ventricular wall. This means that decision may be difficult in a child without cardiac enlargement or cyanosis and in whom the only symptom is dyspnea on exertion.

Tetralogy of Fallot is a combined anomaly, incorporating elements of all three groups Failure of the membranous interventricular septum to close, a simple persistence of a normal fetal stage, is perhaps merely a secondary effect of the stenosis of pulmonary outflow tract which is usually in the infundibular portion of the right ventricular wall, though it may be at the valve as in pure pulmonary stenosis. Typically there is also an abnormality of aortic origin such that it seems to arise partially from both ventricles, straddling or "overriding" the incomplete ventricular septum and receiving blood from both ventricles. This "dextroposition" or partial transposition of the aorta is an anomaly of the third group, not normal at any stage of fetal development and possibly

due to unequal division of the primitive truncus arteriosus. Its extent varies greatly in different individuals.

The term tetralogy of Fallot is primarily a descriptive one, referring to the four features which combine to form the syndrome; dextroposition of the aorta, pulmonic stenosis, ventricular septal defect, and right ventricular hypertrophy. Since it is not a true entity, its manifestations vary widely depending on which anomaly is preponderant. If aortic transposition is preponderant and pulmonic stenosis is slight, there will be deep and almost constant cyanosis due to the ease with which right ventricular blood enters the aorta, rather than the difficulty with which it enters the pulmonary artery. The result may be a situation very similar to Eisenmenger's syndrome, which differs anatomically only in the complete absence of pulmonary stenosis. Such a patient can be helped relatively little by operation.

On the other hand if the aortic overriding is slight, the membranous septal defect small, and the obstruction to pulmonary flow the major factor, the result will be similar to that seen in "pure" pulmonary stenosis. In both situations cyanosis is almost absent at rest, but deepens during exertion through "overflow" from the right heart into the left. Indeed those patients in this group in which the obstruction to pulmonary flow is due to valvular stenosis can best be treated by the Brock procedure. In the majority, however, stenosis is in the infundibular region. Although a direct approach to such a lesion is being investigated by Brock and by Glover, their results are not yet sufficiently consistent to warrant general use. In most cases establishment of a shunt between systemic and pulmonary circulation, as demonstrated by Taussig and Blalock, gives satisfactory and striking relief.

In making the diagnosis, tetralogy must be differentiated not only from the Eisenmenger syndrome and "pure" pulmonary stenosis but also from other anomalies causing cyanosis Most of these anomalies are of very early origin, falling in all three groups. Common ventricle, persistent truncus, atresia of the pulmonary artery, Ebstein's syndrome, and transposition of the great vessels are in this group, and more complex combined anomalies are frequent. A distinguishing feature is the constancy of the cyanosis in the latter group, as contrasted to the variable cyanosis in most cases of tetralogy. The character of the murmurs is of little help, but absence of murmur practically rules out tetralogy. In ad-

dition, heart size and contour on roentgenogram or fluoroscopy is of considerable importance, for the more primitive anomalies usually result in large globular hearts, whereas the heart in tetralogy is rarely enlarged and often presents a characteristic "boot-shaped" contour. Angiocardiograms demonstrate that the right ventricle empties into the aorta, but this may occur in other anomalies. On occasion it may also demonstrate the point of infundibular narrowing. Cardiac catheterization is very useful when the diagnosis is obscure, since from data so obtained the difference in flow between pulmonary and systemic circulation can be calculated This is of great assistance in distinguishing tetralogy from Eisenmenger's complex, and excluding the presence of a compensating patent ductus arteriosus It cannot differentiate atresia of the pulmonary artery, however In general, as Taussig has emphasized, in the majority of cases it is not necessary to resort to the more complicated diagnostic procedures, though they may give a useful measure of the severity of the abnormality and the chances of success in surgical treatment

The Blalock-Taussig procedure consists in establishing a new channel from a systemic artery into the pulmonary. The right subclavian is Blalock's artery of choice, though other surgeons prefer the left. Potts has shown that a direct anastomosis between the aorta and the left pulmonary artery is equally effective. A right-sided aortic arch is present as an accompanying anomaly in about 20 per cent of tetralogy cases, and in these the left subclavian is usually readily available. On occasion other arteries may be used, and at times an end-to-end anastomosis may have to be resorted to, resulting in perfusion of one lung by the pulmonary and the other by a systemic artery

At present it is difficult to deny the benefits of a shunting procedure to any patient suffering from tetralogy. These benefits often convert a cardiac invalid into a patient with only a mild handicap Yet the result is far from a normal situation, and it remains to be determined how long the benefits will last Patients with tetralogy and a compensating patent ductus arteriosus, which is the combination of anomalies that inspired the Blalock procedure, may ultimately develop increasing sclerosis of the pulmonary vessels which nullifies the benefits of the shunt and ultimately proves fatal. A direct attack upon the point of obstruction is a more physiologic approach When this point is the pulmonary valve, a Brock procedure is therefore preferable, yet even under these circumstances,

if there is much overriding, the effect may be only to convert a tetralogy into an Eisenmenger's syndrome. A truly anatomical correction must await perfection of techniques which will allow operations to be carried out under direct vision within the cardiac chambers.

Transposition of the great vessels is the only other anomaly which has been treated surgically with any success. This condition is incompatible with postnatal life unless there is also another anomaly which permits mixing of the venous and arterial blood. Often in surviving infants this opening is in the auricular septum and in some instances it may be relatively small and ineffective. Blalock has reasoned that these patients should be helped by establishing a new and larger opening and has perfected a technique for accomplishing this by creating a window between pulmonary vein and right auricle. He reports fair results in children but a high mortality in infants. This is a procedure admittedly still in the experimental stage and a problem fraught with many difficulties.

The challenge to perfect new methods to deal with the as yet uncorrectable anomalies is very great, for it has been proved that the heart of a child so afflicted can often be manipulated without disaster if certain essential requirements are met. Chief among these is an adequate continuous oxygen supply to the myocardium. The body must also receive a constant adequate circulation of oxygenated blood, and must at the same time rid itself of excess carbon dioxide. Thus skillful anesthesia is of utmost importance. It is known that healing of sutured blood vessels or myocardium is rapid and that new endothelium grows quickly over suture lines or grafts or nonirritating foreign material provided the flow of blood over them is smooth and swift. Hemorrhage can be successfully counterbalanced by adequate transfusion, if necessary given rapidly into peripheral arteries. But the circulation cannot be stopped even for a few minutes, and this fact at present limits intracardiac surgery to blind procedures carried out within the channels of the flowing blood stream.

This challenge has been accepted in numerous laboratories. Much work has been devoted to developing methods for temporarily carrying on circulation with mechanical devices outside the body with or without providing for gaseous exchange. Although it is possible to substitute a mechanical device for one side of the heart only, relying on the patient's own lungs for ventilation, such a device would have little usefulness in making possible operations to close openings between auricles or

ventricles The workers, especially Gibbon, who have succeeded in mechanically maintaining both circulation and respiration in animals are approaching a more practical solution. If this could be found, a new era of truly intracardiac surgery would begin, and many of the anomalies now beyond reach of the surgeon might come within his control. At present he can work only peripherally or blindly, but even within these limits he has added greatly to his understanding of the pathological physiology of the circulation, while at the same time restoring many patients heading for early death to comparative or complete health.

THE ELECTROCARDIOGRAPHIC EFFECTS OF MYOCARDIAL AND PERICARDIAL INJURY*

Charles E. Kossmann †

"IT IS PROBABLE that [the string galvanometer] will give information of much value where the action of the heart, as a whole, is perfectly regular, and where the contraction, originating at the normal site of impulse formation, namely the sino-auricular node, progresses at normal rates through the heart and along definite and recognized channels."

This prophecy, from a paper by Lewis and Gilder (1), was made in 1912 after the authors concluded that the "new chapter in clinical medicine" which resulted from the use of the instrument in "deciphering" irregularities of the ventricles and disorders "in the sequence of contraction in its chambers" was rapidly closing.

The prophecy has been amply born out in the four decades since it was made. Lewis had in mind the modifications in the electrocardiogram which he recognized to occur with hypertrophy. He lived long enough to see the string galvanometer give much more valuable information than his earliest observations made him suspect it would.

A great many investigations have contributed to the present-day understanding of the alterations in the electrical behavior of the myocardium which are reflected in recognizable modifications of the electrocardiogram. The most significant of these have been the studies, almost exclusively by F. N. Wilson and his school (2), on the laws governing the behavior of an electromotive force in a volume conductor. The results

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Original investigations quoted were aided by grants from the New York Heart Association and the Knapp Foundation.

of these original studies have been modified only slightly by subsequent investigations. Only a few problems remain to be solved in this area. If the year 1912 was regarded as the end of the era of the arrhythmias, the mid-twentieth century may be regarded as the time when the chapter on the effects of the body regarded as a volume conductor may be considered to be coming to a close.

A discernible third period, already well along, and destined almost certainly to have clinical repercussions, is concerned with the intensive study of the source of the electromotive force itself, namely, the myocardial cell. Because an understanding of the electrical behavior of the cell is fundamental to an understanding of the electrocardiographic effects of myocardial and pericardial injury seen clinically, a résumé of pertinent facts will be given.

The Cell

To begin with it is customary to accept Bernstein's membrane theory (3), proof of which, with some modifications from the original, is convincing. The theory states that the resting cell possesses a membrane which is semipermeable to ions. These are oriented in such a way that the outside of the resting cell is electrically positive and the inside negative with reference to ground potential.

The difference in potential across the membrane has been measured in the squid giant axon (4, 5), and in the sartorius muscle (6, 7) and the myocardial cell of the frog (8). In these tissues it averages 45 to 88 mv. It is called the "resting membrane potential."

When the cell undergoes stimulation, natural or artificial, depolarization of the membrane occurs presumably due to a change in permeability to ions or other charged particles. The original potential not only disappears but reverses slightly (about 30 per cent) so that the membrane potential is temporarily opposite in polarity, but in less degree, to the resting state. It is very probable that this "overshoot," as it is called, is comparable to the phenomenon of the same name known to occur in electrical condensers, and may be due to inductance (4) with a temporary realignment of electrons on the membrane, the reverse of what is found in the resting state.

Following the rapid depolarization there is a gradual restoration of the original membrane potential with varying speeds as shown in the varying

Chapter 11

THE ELECTROCARDIOGRAPHIC EFFECTS OF MYOCARDIAL AND PERICARDIAL INJURY*

Charles E. Kossmann†

"IT IS PROBABLE that [the string galvanometer] will give information of much value where the action of the heart, as a whole, is perfectly regular, and where the contraction, originating at the normal site of impulse formation, namely the sino-auricular node, progresses at normal rates through the heart and along definite and recognized channels"

This prophecy, from a paper by Lewis and Gilder (1), was made in 1912 after the authors concluded that the "new chapter in clinical medicine" which resulted from the use of the instrument in "deciphering" irregularities of the ventricles and disorders "in the sequence of contraction in its chambers" was rapidly closing.

The prophecy has been amply born out in the four decades since it was made Lewis had in mind the modifications in the electrocardiogram which he recognized to occur with hypertrophy He lived long enough to see the string galvanometer give much more valuable information than his earliest observations made him suspect it would.

A great many investigations have contributed to the present-day understanding of the alterations in the electrical behavior of the myocardium which are reflected in recognizable modifications of the electrocardiogram. The most significant of these have been the studies, almost exclusively by F. N Wilson and his school (2), on the laws governing the behavior of an electromotive force in a volume conductor. The results

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of the negative intracellular potential as the electrode is withdrawn from the cell, after which it is close to the surface of the heart and records a small ventricular complex (QRS) or "axial current" (10, 11). Part C shows a slower slope to repolarization and a drop of potential below its original intracellular level or "hyperpolarization."

It is noteworthy, for its clinical interest, that temperature has little effect on the voltage of the membrane action potential but the rate of depolarization is quite sensitive to this variable, being longer the lower the temperature (8, 12).

From these remarks it is clear that the action potential of the cell may be, if desired, divided into at least five phases: 1) depolarization, also called excitation, accession, or invasion, which represents a period of increasing activity of the cell, 2) overshoot, which is probably a condensation phenomenon on the membrane; 3) complete activity or possession partly obscured in direct cellular experiments by the gradual "leaking off" of the overshoot, 4) repolarization, also called recovery, regression, or retreat, which represents a period of decreasing activity of the cell; 5) hyperpolarization. The overshoot and the hyperpolarization may not be essential parts of the electrical process. In any case they may, for didactic purposes, be disregarded temporarily and the electrical activity of the cell defined as a tripartite one, consisting of accession, possession, and regression (13).

The Conducting Medium

The relatively simple monophasic curve obtained during the study of the membrane action potential of a cell is altered when the electrode used to record it is moved to the exterior of the cell, and is separated from it by part of the physiological conducting medium Analysis of the effects are possible because the accession process or period of increasing activity of the cell behaves as though it were a dipole or double electric layer with the positive pole or side facing the direction of excitation of the muscle This results from the fact that with activity, as already shown, the polarity of the cell membrane decreases Another way of saying this is that the density of charges on it is decreased. The resting muscle just ahead of the active muscle, being more densely polarized, behaves as though it were positive electrically with respect to the active portion. The regression process or period of decreasing activity may be regarded

slopes of the recovery curve. Sometimes there is at the end of recovery a slightly greater negative potential than before. This is temporary and is spoken of as "hyperpolarization" (9).

These collective phenomena, known as the "membrane action poten-

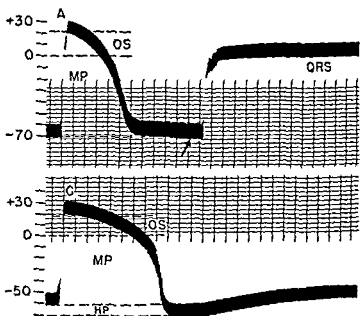


Figure 20 Action potentials of single cardiac ventricular fibers (MP, Resting membrane potential, OS, Overshoot, HP, Hyperpolarization) All measurements made from bottom of string shadow Ordinates—millivolts, abscissae—time. Vertical lines 0.1 second apart.

A. Action potential of single ventricular fiber Arrow indicates start of withdrawal of electrode from cell to show return of string to zero value and presence of small surface electrocardiogram (QRS).

C. Action potential of longer duration.

(Woodbury, L. A., Woodbury, J W, and Hecht, H H "Membrane resting and action potentials of single cardiac muscle fibers," *Circulation*, 1:264–66, 1950.)

tial" are shown as they occur in the myocardial cell of a frog in Figure 20 taken from the paper by Woodbury, Woodbury, and Hecht (9). Part A of this figure shows a membrane potential in the myocardial cell of a frog of 70 mv. As excitation proceeds over the cell there is an overshoot of 30 mv with a gradual return to the original large negative potential as the repolarization proceeds slowly at first, more rapidly toward the end of systole. This part of the figure also shows the disappearance

diagrams in Figure 21 From the upper formula and diagram, it is clear that the potential (or size of the deflection in the finished record) will be larger the closer the dipole is to the point of recording (the shorter the distance, R). Also an elementary knowledge of trigonometry will make it obvious that as the angle θ approaches o degrees, the effect on the electrode, E, in the conducting medium will be maximum and positive. At 180° it will be maximum and negative. In the lower part of the figure, the effect of the charged membrane or double electric layer on electrode E will be greater as the area of the membrane is larger, and the distance between it and the electrode is smaller. These two variables are measured by the angle ω which is a solid angle subtended on a sphere of unit radius drawn about the point (E in figure) in the conducting medium being studied The value, Ø, is determined by the number and the magnitude of the charges on the membrane

The dipole or the double electric layer may be represented by a vector with an axis parallel to the axis of the dipole, or normal to the surface of the charged membrane Its length is made proportional to the size of the electromotive force involved

With either of these methods of analysis, then, the simple intracellular monophasic curve is converted into a more complicated extracellular, quadriphasic curve, as *shown in Figure 21*, where accession and regression are regarded as dipoles (upper figure) or double electric layers (lower figure) The asymmetry of the accession deflections (QRS) and the regression deflections (S-T and T) as shown in the figure *is* attributable to the special circumstance that the electrode in this instance is placed at the distal end of the strip These two sets of deflections would be symmetrical if the lead was made from the middle of the strip (13).

In a lead from the medium surrounding the isolated strip of muscle the processes of accession and of regression are equivalent Although the latter process takes longer, the voltages involved are less, and the product of the two (time x voltage) is identical with, though opposite in sign, to a similar product for accession. This is the same as saying that the area of QRS is equal to the area of the T wave, and that the sum of the two is zero In the electrocardiogram of the normal human ventricle the area of QRST is not equal to zero because certain variables are operative which delay the regression process in various regions of the ventricular muscle (14), more particularly the subendocardial regions (15) These

similarly but with the polarity reversed since the active muscle precedes the resting muscle. Under such circumstances, provided the medium is homogeneous (2), the effects of the dipole or double electric layer on an electrode or point in the medium may be analyzed by the formulas and

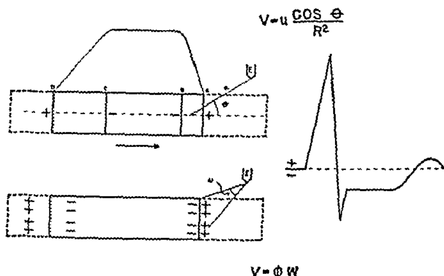


Figure 21 Methods of analyzing the effect of the membrane action potential on a unipolar lead in a homogeneous conducting medium

The cell is shown diagrammatically twice, with the source of electrical energy in depolarization (AB) and repolarization (CD) being regarded as a dipole in the upper figure, and as a charged surface or lamina (double electric layer) in the lower figure In the former the potential of the electrode, E, is defined by the upper formula in which μ is a constant which depends on the distance between the dipoles and the quantity of charge they carry. R is the distance from the center of the dipole to the electrode E, and θ is the angle between R and the positive side of the axis In the latter the potential, V, of the electrode, E, is defined by the lower formula in which φ is a value which depends on the density of the charges on the membrane and ω is a solid angle subtended on a sphere of unit radius about E. Polarity of the electrode is determined by the side of the charged membrane seen by an observer stationed at E.

On the upper cell is drawn the membrane action potential as recorded in Figure 20, with the omission of the overshoot and the negative after-potential (hyperpolarization). The diagrammatic electrogram on the right is the record obtained by the electrode in the conducting medium as a result of the changes in the electrical field of the medium brought about by the membrane action potential. The inequality of the positive and negative phases of this quadriphasic curve is ascribed to the special circumstance of the recording electrode being at the end of the cell opposite the point of stimulation

surface of that chamber. An initial negative potential results which manifests itself as a Q wave in the unipolar lead from either or both extremities or in the bipolar leads (I, II, III) in which these extremities are used The principles also apply to the precordial leads (17, 18, 19).

The lesser degrees of injury are more complex, and knowledge of the basic electrophysiology concerned is still incomplete. However, an at-

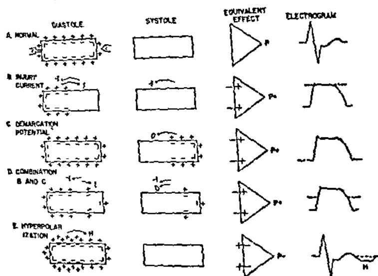


Figure 22 Some of the theoretical types of injury which may modify the electrical behavior of the cell The equivalent effect is shown as the effect of a simple charged membrane or lamina on a point, P, in a surrounding conducting medium according to the formula $V = \phi\omega$ (see Figure 21 and text). The electrograms display the phase in which the effect will be manifest, and its nature. E, electrode, S, stimulator, I, injury current; −I, compensating current, D, demarcation current; H, hyperpolarization

tempt can be made to classify what is known with the full realization that some of it is tentative depending on further investigations.

In addition to the type of injury which modifies QRS, there are at least six additional types which are reflected electrocardiographically in abnormalities of the S-T segment, the T wave, and perhaps the U wave. In discussing these, reference to the changes in a single cell will be made for the sake of simplicity. It is clear, however, that the discussion also applies to any aggregate of cells

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differences in duration of the excited state are accurately measured by the area of QRST which, when reduced to a quadrential vector, indicates the direction and magnitude of these differences. Its direction is from an area where recovery is longest to an area where it is shortest. It is known as the ventricular gradient.

Specific Electrical Effects of Injury

In any discussion of the effects of myocardial and pericardial injury on the electrocardiogram, there is one explanation which must be made at the outset, namely the definition of the word "injury." The term, as applied to the myocardium, is used loosely, and a concept of its meaning will depend largely on whether one is a clinician, pathologist, embryologist, or microbiologist. For the purposes of this discussion, injury may be regarded as *any process which either completely abolishes or only modifies, singly or in combination, the rate, course, or extent of the cellular processes of depolarization and repolarization.*

Preliminary to this discussion, too, it is desirable to note that the total electrical effect of a resting cell on a point in a surrounding medium is zero (Figure 22A) because this "double layer," being completely closed, has no boundaries The solid angle subtended by it on a point in the surrounding medium is really the sum of two identical solid angles subtended by the same imaginary boundary but of opposite sign. The sum of these and the potential of all points in the medium are obviously zero (2, 16, 17).

Having some knowledge of what happens in the normal cell during electrical activity, the problem to be considered logically is how does injury, as defined, modify these processes.

The answer appears to depend largely on the degree of injury. The easiest degree to understand is the injury which results in complete functional and usually anatomic destruction of the cell. Such a cell no longer contributes an electromotive force of any kind. Its absence is reflected in the clinical electrocardiogram by changes in the initial ventricular deflections, QRS, since the dead cells no longer contribute to the mean manifest potential of ventricular depolarization which these deflections reflect. Since clinical death of myocardium is frequently extensive, the absence of the cells results in either the left arm or left leg becoming in effect a total or partial semidirect lead from the cavity of the left ventricle, where normally they were semidirect leads from the

surface of that chamber. An initial negative potential results which manifests itself as a Q wave in the unipolar lead from either or both extremities or in the bipolar leads (I, II, III) in which these extremities are used. The principles also apply to the precordial leads (17, 18, 19).

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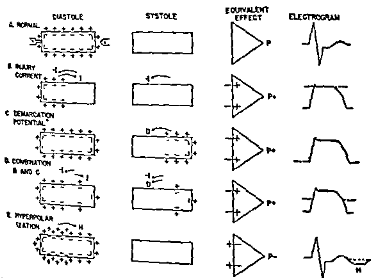


Figure 22. Some of the theoretical types of injury which may modify the electrical behavior of the cell. The equivalent effect is shown as the effect of a simple charged membrane or lamina on a point, P, in a surrounding conducting medium according to the formula $V = \phi\omega$ (see Figure 21 and text). The electrograms display the phase in which the effect will be manifest, and its nature. E, electrode, S, stimulator, I, injury current, —I, compensating current, D, demarcation current, H, hyperpolarization.

tempt can be made to classify what is known with the full realization that some of it is tentative depending on further investigations.

In addition to the type of injury which modifies QRS, there are at least six additional types which are reflected electrocardiographically in abnormalities of the S-T segment, the T wave, and perhaps the U wave. In discussing these, reference to the changes in a single cell will be made for the sake of simplicity. It is clear, however, that the discussion also applies to any aggregate of cells.

The best understood of these injuries is one which results in partial or

complete depolarization of a part of the cell. The resting membrane potential in the injured area is of lesser magnitude, and hence this injured part is electrically negative with respect to uninjured parts (Figure 22B). During diastole a current flows from the uninjured to the injured region known as the current of injury (1). The electrical effect is equivalent to a double electric layer with the negative side toward the injured region (2). Since it is assumed to be constant, and may, for purposes of discussion be regarded as balanced by a compensating current from the galvanometric circuit (-I in Figure 22B), the current involved causes no discernible deflection of the galvanometric recorder during diastole. But if the entire cell should be abruptly depolarized by normal activity, the recorder will deflect during systole to a degree proportional to the magnitude of the original current of injury, and in a direction determined by the location of the electrode with respect to the injured and uninjured regions. The S-T segment will be displaced (Figure 22B) not by the original current of injury (designated I) but rather by an equivalent double layer oriented in the reverse way, called —I (20). If the exploring electrode is nearer the injured than the uninjured side of the cell as shown in the figure, the displacement of the S-T segment will be upward or positive and toward the original baseline before the current of injury displaced it

Theoretically, and clinical evidence of several kinds supports it, a degree of injury may exist in which the resting cell shows no abnormality, but depolarization of it may not be complete (Figure 22C). The wave of excitation may be regarded as being blocked at the injured site and acting there as a standing wave or interface with its positive surface toward the injured region. As with the current of injury, the S-T segment will be elevated when the electrode is on the positive side of it, but in this instance a new current, D, dependent on the existence of a demarcation potential,* is flowing during systole rather than abolished. It can be represented as a change of the baseline to a new positive level if the exploring electrode bears the same relation to the cell as in the

* The term, demarcation potential, is used by the neurophysiologist (21) to describe the difference in electrical energy which results from differences in electrical properties of adjacent segments of nerve, and in this sense includes injury potentials. For the purpose of this presentation, demarcation potentials and injury potentials, and the currents which result from them, are regarded as differing from each other in the manner depicted in Figure 22B, C, and D

previous example. To be noted is that the equivalent electrical effect is the same as if a current of injury were assumed to exist during diastole (Figure 22B and C). It is this mechanism which is suspected of being responsible for the displacement of the S-T segment which may occur spontaneously or following effort or induced hypoxemia in patients with anginal syndrome. It is also believed to be the mechanism involved when pressure is made on the endocardium with the cardiac catheter.

A fourth type of injury is theoretically possible (Figure 22D). It is a combination of the second and third types. The equivalent effect is similar to, but larger than, the equivalent effect of either of the previous two types individually. In clinical infarction it is very probable that this combination is involved.

The fifth type of injury has been seen during the use of the electrode catheter. It consists of a large long negative potential occurring in diastole, and at a time when a U wave, if present, would appear It is suggested that this phenomenon is caused by hyperpolarization such as seen in some of the experiments on the cell The probable electrical situation is shown schematically in Figure 22E.

A sixth type of injury which is difficult to illustrate diagrammatically is of considerable clinical significance and has been ascribed to ischemia (20) It is a degree of injury which does not result in subnormal repolarization or depolarization but rather in a delay in the rate of repolarization in some part of the cell (or in some part of the heart) This difference in the duration rather than magnitude of the excited state results in an abnormal final deflection or T wave. This "gradient" in the rate of recovery is accurately defined, as noted above, by the vectorial sum of the mean vectors representing depolarization and repolarization In the clinical electrocardiogram it is determined from the area of QRS and T. In Einthoven's triangle (frontal plane of the body) its direction is usually such as to make an angle with the horizontal (angle α) of 0° to 90° and its mean length is approximately 50 microvolt seconds (μvs).

Clinical Considerations of Myocardial Injury

Because of the limited definition of injury made earlier, no discussion will be included of such electrocardiographic manifestations of injury as atrial and ventricular dysrhythmias, and atrioventricular and intraventricular block

From what has been presented thus far it must be clear that the knowledge now possessed regarding the individual cell is applicable with only slight modification to an aggregate of cells or the heart as a whole.

In the atria. The atria differ from the ventricles in that no specialized conduction system is believed to exist for them. This makes the problem easier in that the atrial muscle may be regarded as a large syncytium over which excitation and recovery pass in a radial manner from the pacemaker, the sinoatrial node.

It has been shown experimentally that the accession and regression processes behave as though they were dipoles or double electric layers proceeding across the muscle. If the wave of accession behaves as a dipole with the positive pole in the direction of movement, and the wave of regression behaves as a dipole with the negative pole in the direction of movement, then a quadriphasic curve would be expected, as noted earlier, when an electrode is placed directly on or close to the endocardial or epicardial surface of the atrium. In order to free the curve of the electrical effects of the normally sequential ventricular deflections, efforts to demonstrate this should be made preferably in a heart displaying a long atrioventricular conduction time or even complete atrioventricular block A record from the atrium of a patient with the latter defect in conduction was made (Figure 23) The rapid initial accession deflections are easily recognized as being diphasic, with the first phase (a_1) positive and the second (a_2) negative. The regression deflections are smaller but longer with the first (r_1) negative and the second (r_2) positive. The period of possession (a_2 to r_1) is very brief.

The patient had arteriosclerotic and rheumatic heart disease, and at necropsy the right atrium was abnormally large The atrial electrogram cannot, therefore, be accepted as a normal but it does demonstrate the basic electrophysiology involved which agrees, with the exception of the U wave, with the experimental findings in the frog's atrium made by Macleod (13). The U wave, positive in this instance, may be on the basis of inductance in the nonexcitable endocardium brought about by the trailing edge of the wave of regression.

When the electrode makes pressure on the endocardial surface of the atrium, the curve becomes distorted in a characteristic way (Figures 24 and 25). The junction between the initial and final atrial deflections ($S\text{-}T_p$ junction or Jp) invariably becomes elevated, and the initial de-

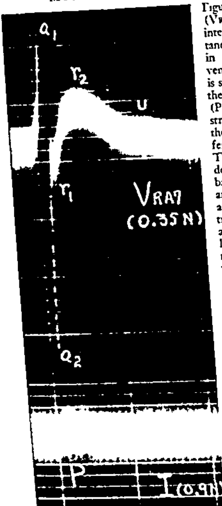


Figure 23. An enlarged electrogram (V_{RA}, upper record) made from the interior of the right atrium simultaneous with lead I (I, lower record) in a patient with complete atrioventricular block The lower record is somewhat distorted by "hum" but the relatively simple, notched P wave (P) can be seen. Its actual complex structure at its source can be seen in the upper record in which five different deflections are recognizable. The waves a_1 and a_2 are the accession deflections (Macleod); the latter is barely visible. The waves r_1 and r_2 are the regression deflections which are of reverse direction, longer duration, and lower amplitude than a_1 and a_2. The slow terminal positive wave labeled U is of unknown origin The rapid change from a_1 to a_2, which was so rapid it was not photographed, is the "intrinsic deflection" which delineates the period of increasing activity of the cell (depolarization or rapid disappearance of the membrane potential, Figures 20 and 21, AB) The slower change from r_1 to r_2 delineates the period of decreasing activity of the cell (repolarization or slow restoration of the membrane potential, Figures 20 and 21, CD)

Time lines occur every 0 2 second The figures, 0 35N and 0 9N, indicate the sensitivity of the respective strings when the records were made (Kossmann, C E "The interpretation of unipolar precordial electrocardiograms," *M Clin North America*, 34 833–55, 1950)

flections (QRSp) may be modified usually by a reduction in the size or obliteration of the S_p wave. The duration of recovery (J-T_p interval) appears to be lengthened All of the phenomena disappear promptly when the electrode either spontaneously or by design no longer makes pressure on the endocardium The modifications of the initial and final atrial deflections may be encountered in either atrium They have been observed when the catheter was in the coronary sinus or one of its venous

tributaries, and have been seen intermittently with atrial flutter (Figure 26).

The phenomenon is attributed to a block of the wave of depolarization at the electrode so that the latter is electrically positive during systole.

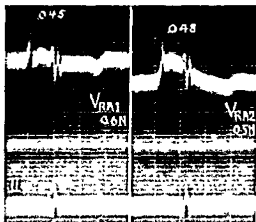


Figure 24. Right atrial electrograms (V_{RA_1} and V_{RA_2}) recorded from adjacent points in the right atrium of a normal man simultaneously with lead II (II) The second differs from the first by the presence of a contact or demarcation potential manifested by an elevation of the S-T segment which extends through and displaces the initial ventricular deflections, QRS, but has no effect on standard lead II.

The figures, 0.45 and 0.48, indicate the time in seconds between the beginning of the P wave in lead II and the beginning of the intrinsic deflection in the electrograms The figures, 0.6N and 0.5N, indicate the fraction of normal sensitivity of the string galvanometer used when the records were made Time lines, 0.2 second.

The situation is thought to be comparable to what is shown diagrammatically in Figure 22C, with the probable addition (not shown) of a slower rate of repolarization. The electromotive force generated under such conditions is sharply localized to the exploring electrode itself and does not affect the S-T_p segment of a simultaneous standard lead or precordial lead made over the intracardiac electrode. It is doubtful that a current of injury exists during diastole (Figure 22B) because the force under consideration, which may be regarded as arising from a demarcation potential or pressure potential, promptly disappears when pressure on the endocardium is released. This is in contrast to the injury current which is ascribed to a more serious degree of impairment of electrical function caused by actual depolarization of part of the cell or some of the aggregate of cells. It disappears gradually over a period of time as the injured cells either undergo necrosis or recover.

There appears to be no spontaneous clinical counterpart of the atrial demarcation current as observed with the catheter. However, injury potentials, theoretically at least, can exist with infarction of the atrium

or involvement of it by inflammatory or neoplastic disease. Whether the P-R segment, measured from the end of the P wave to the beginning of ventricular QRS, is elevated or depressed as a result of such injury potentials will depend on the orientation of the electrodes used in the surface lead with respect to the equivalent double electric layer resulting from the injury (Figure 22B). It must be kept in mind, too, that the P-R segment will be displaced by such factors as digitalis and tachycardia by

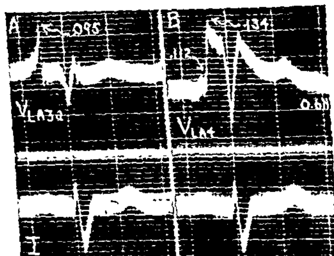


Figure 25 Left atrial electrograms $V_{LA_3}a$ and V_{LA_4}) recorded (from adjacent points in the left atrium of a man with an atrial septal defect simultaneously with lead I Record B shows the distortion caused by contact of the electrode with the endocardium Numbers and time lines are as in Figure 24.

virtue of their effect on the regression process in the atria Theoretically the P wave itself may be modified in form if destruction of atrial musculature is extensive

The incidence of infarction in the atria is higher than most pathological data indicate. In the series studied by Cushman, Feil, and their associates (22) there were 31 instances (17.0 per cent) of atrial infarction among 182 cases of myocardial infarction The great majority (21 cases) were in the right auricular appendage and were accompanied by mural thrombosis as well Although the majority displayed abnormalities of the atrial mechanism, only five displayed depression of the P-Q segment. Other

reports of alterations both in P wave and P-Q segment have been made, and one experimental study of the effects of alcohol-induced necrosis (23) suggests that the P-Q segment may be elevated in lead I with left atrial injury, and elevated in leads II and III with right atrial injury, both

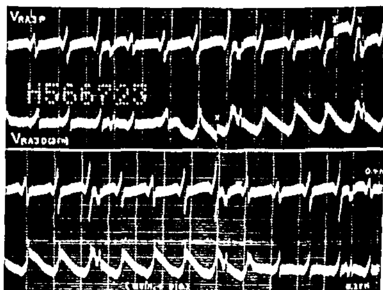


Figure 26. Atrial flutter with intermittent demarcation potential. The record is a continuous one A double electrode catheter was used. Each electrode was 1 mm in length, and the distal ends of the two were separated by a distance of 3 cm. The electrogram from the proximal electrode (V_{RA_3},P) shows no distortion of the S-T segment, although there is some variation in the initial atrial deflections probably caused by movement of the electrode The electrogram from the distal electrode (V_{RA_3},D) shows a spontaneous occurrence of displacement of this segment toward the end of the upper strip and a spontaneous disappearance at the end of the lower The x marks points at which a standardizing current was passed through the string. Ventricular deflections may be recognized as occurring in a ratio of 1 4 to the P waves. The patient was receiving quinidine and digitalis Time lines, 0 2 second.

accompanied as well by a change in amplitude and form of the P wave. *Clinical confirmation of this finding has not been forthcoming.*

With neoplastic involvement of the atria (24) disturbances of rhythm seem to be more common than abnormalities of the initial or final atrial deflections.

In summary, it may be stated that experimental and clinical studies of the electrical behavior of the atrial myocardium have been most valuable

in elaborating and crystallizing the present state of knowledge concerning the normal and abnormal electrophysiology of the heart. The practical use of this information as applied to the atria has been limited because of the relative infrequence of dynamically important disease of these chambers, and the dominance of rhythmic disturbances rather than electrocardiographic abnormalities resulting from a change in the extent, rate, or course of depolarization or repolarization.

In the ventricles As in the right atrium, demarcation potentials may be

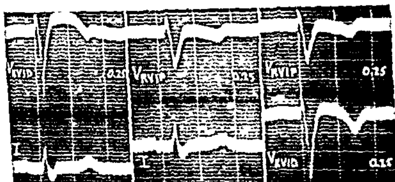


Figure 27 Endocardial potentials of the right ventricle in a patient with right bundle branch block The double electrode catheter was used with electrodes 3 cm apart The first record ($V_{RV,D}$) recorded from the distal electrode simultaneously with lead I (I) shows elevation of the S-T segment. The record from the proximal electrode ($V_{RV,P}$) shows no distortion of this segment When the recording was made simultaneously from the two intracardiac electrodes (third record), some but not all of the S-T elevation had spontaneously subsided. Time lines, 0 2 second

encountered during catheterization of the right ventricle (25) or of the left ventricle (26, 27) These are accompanied by a variety of modifications of the preceding deflections of depolarization Sometimes the initial positive deflection and deep, notched negative deflection characteristic of a right ventricular lead are not modified at all or only slightly by the demarcation potential (Figure 27), in other instances the S wave is almost completely eliminated, making the curve appear, in a sense, monophasic (Figure 28) It is suspected that obliteration of the QRS deflection is largely an algebraic effect on the electrode of two oppositely oriented double electric layers The contact potentials are not reflected in surface leads (Figure 29).

As in the atria, no exact clinical counterpart of this catheter pressure potential occurs unless it be the rare example of a tumor (28) or foreign body pressing on the heart, or the abnormal mechanics at the margins of a ventricular aneurysm (29). A degree of excitation block is regarded as accompanying *all* injury currents by some (30). *It is likely that the temporary S-T displacements seen in anginal syndrome are on this basis,*

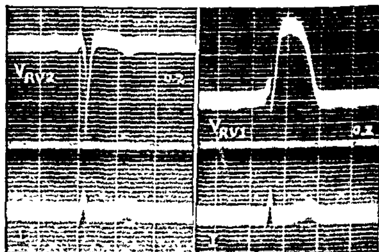


Figure 28 Leads from adjacent points in the right ventricle of a normal man showing the "monophasic" distortion which occurs (V_{RV_1}) when the electrode makes pressure on the endocardium The similarity of the earliest parts of QRS in both records is to be noted. The simultaneous lead is I, recorded at somewhat less than normal sensitivity with V_{RV_2}. Time lines, 0 2 second (Kossmann, C. E., Berger, A R., Rader, B., Brumlik, J , Briller, S A , and Donnelly, J H. "Intracardiac and intravascular potentials resulting from electrical activity of the normal human heart," *Circulation*, 2.10–30, 1950.)

the block being induced by a relative vascular insufficiency of short duration.

On the other hand, injury phenomena of longer duration are common in the ventricles and, *depending on the degree, may modify* the QRS deflections, the S-T segment, the T wave, or combinations of these.

The changes which occur in QRS, other than those caused by intraventricular block, are due to the loss of muscle elements which ordinarily contribute to the total of the deflections resulting from depolarization of the ventricular muscle The best-known change, alluded to earlier, is the subendocardial or transmural destruction of the wall of a chamber,

usually the left ventricle, resulting in a surface lead becoming a partial or complete semidirect lead from the cavity of that chamber.

One of the earliest changes in the electrocardiogram which occurs with coronary closure is rarely seen in clinical curves but has been produced in animals (31). When a coronary artery is tied off in a dog the initial change is in the T wave, not in the S-T segment. This is ascribed to ischemia with a delay in the velocity of the repolarization process in

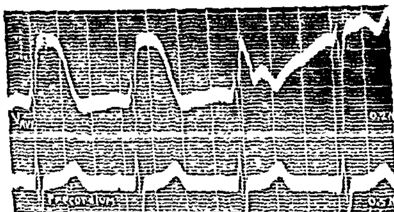


Figure 29 Contact potential shown in a lead (V_{RV}) from the cavity of the right ventricle of a normal man which disappears as the electrode is slowly withdrawn. The distortion of the baseline at the end of the trace is presumed to be due to breaking the endocardial contact The last complex is probably a record of the true cavity potential before distortion. The simultaneous lead made with an electrode placed on the chest wall directly over the intracardiac electrode shows no change as the demarcation potential is made to disappear. Time lines, 0 2 second

the involved muscle As the ischemia becomes more severe, necrosis results, and there is then superimposed the effects of an injury current which tend to displace the S-T segment in a direction opposite to the abnormal T wave. Once the injury current subsides, as the cells responsible for it either die or recover, the S-T segment returns to the baseline, and the delayed recovery in the "ischemic" muscle adjacent to the dead zone again results in abnormal T waves of a type which are well known clinically

An observation of some interest and without a satisfactory explanation is the occurrence of elevation of the S-T junction and segment in

precordial leads when there is infarction in the anterior part of the heart, and depression of this junction and segment when there is infarction in the posterior part of the heart. The spatial axis of injury, E_J, points upward, forward, and to the left in the anteroseptal infarct (Figure 30B);

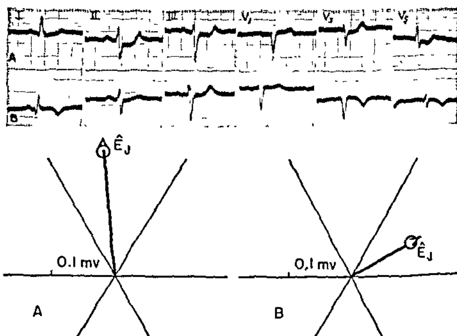


Figure 30. Changing spatial axis of injury, E_J, in a male patient with recent myocardial infarction Record A was made approximately two hours after, and record B 40 hours after symptoms began. The initial spatial axis of injury is directed upward, backward, and to the right as expected with a subendocardial lesion The final axis of injury is upward, forward, and to the left as usually seen with infarction in the anterior part of the heart The change is ascribed to the lesion becoming transmural, which is supported by the changes in QRS which have occurred between the two curves Time lines, 0 4 second (see Figures 32A and B).

downward, backward, and to the right in the posteroseptal infarct (Figure 31). On theoretical grounds (Figure 32A) the reverse should be the case because infarction in the heart is usually more extensive on the endocardial than on the epicardial surface, and a good many do not extend to the epicardial surface at all. Under such circumstances the exploring electrode, in the case of an anterior subendocardial infarct, should be on the normal side of a junction between normal and injured tissue. During

electrical systole the electrode would then be negative with respect to surrounding medium as a result of the vector, E_J (or —I), being directed away from the normal muscle (Figure 32A).

Several explanations have been given. Bayley (20) pointed out that with transmural infarction a subendocardial layer of healthy muscle is preserved, under which circumstances the normal-injured junction would have a reverse orientation of that expected on the basis of the distribu-

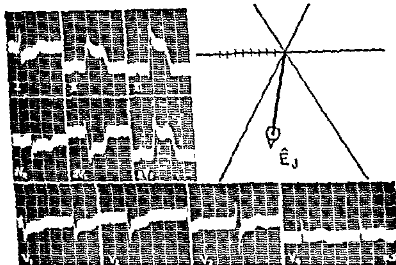


Figure 31 Unusual displacement of the S-T segment in an elderly female after myocardial infarction The spatial axis of injury, E_J, has a direction downward, backward, and to the right as expected in posteroseptal infarction Changes in QRS are not yet fully developed.

tion of the coronary blood supply In experiments on turtles and dogs, Pruitt and Valencia (32) demonstrated that preservation of a subendocardial layer is not essential to the production of an elevated S-T junction in direct or semidirect epicardial leads from an area of myocardial destruction In their experiments, positive displacement was also observed when an electrode was placed on the cavity side of a transmural lesion. They attributed upward displacement of the S-T segment on both aspects of the lesion to boundaries developed between injured and uninjured muscle at the margins of their experimentally produced lesions (Figure 32B)

Rarely in the course of myocardial infarction in the anterior part of the heart a transition is seen in serial records between the theoretically expected downward displacement of the S-T segment in precordial leads and the more usually encountered upward (positive) displacement of this segment. This is demonstrated in Figure 30. The initial record, A, was made approximately two hours after the onset of the clinical syndrome of coronary occlusion with myocardial infarction in a middle-aged man. In it the S-T junction and segments are depressed in the standard and precordial leads. The spatial axis of injury (20, 33) or instantaneous

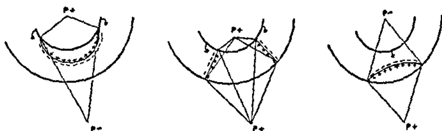


Figure 32. Diagram of the electrical effects of a subendocardial, transmural, and subepicardial lesion The semicircular diagrams represent a portion of the ventricular wall The stippled areas are dead, the clear areas healthy muscle, and between the two is assumed to be an injured area where excitation is *blocked* as it approaches it from the endocardial surface (arrows) The variable electrical effect on points, P, inside and outside the chamber, are on the basis of the relationship, $V = \phi\omega$ (see Figure 21)

vector for the S-T junction, F_J, is directed upward, to the right, and backward. This is the direction expected with a subendocardial lesion (Figure 32A) and is the usual direction taken by this vector when temporary angina occurs spontaneously, is produced by hypoxia or exercise (34, 35), or occurs with tachycardia, hemorrhage, or peripheral circulatory failure in the syndrome called coronary insufficiency (36, 37, 38). Approximately 48 hours later, however, (Figure 30B) the S-T junctions have the more usual reciprocal displacement in the standard leads I and III with elevation in lead I and in the left-sided precordial leads. The vector has changed to an anterior, upward, and leftward direction. The change is ascribed to early involvement of subendocardial

muscle only, similar to what is shown diagrammatically in Figure 32A, and to later transmural involvement, as shown diagrammatically in Figure 32B.

One of the problems of clinical electrocardiography has been the difficulty of telling whether myocardial injury is present when there is a complete defect in conduction in the left bundle branch. The problem is best illustrated by an example (Figure 33) of a patient who had a recent infarct of the heart, and who displayed intermittent left bundle branch block, as well as atrioventricular block, over a period of several days The figure shows the forms of the QRS and T waves with and without block. Lead V_2 shows how the broad, deep T wave caused by delayed subepicardial repolarization is completely obscured and replaced by an upright T when block of the bundle develops. A similar phenomenon, in lesser degree, is displayed by the other leads.

The case relates to the matter of the ventricular gradient (14, 39), already touched upon in the discussion of the electrical behavior of the cell. Stated as simply as possible, the T wave may be modified by two known variables. First, it may be modified by a change in the mean direction of excitation, or QRS Under such circumstances it follows that the mean direction of recovery must of necessity also be changed. This is illustrated by the considerable alteration in the T wave which occurs where there is intermittent bundle branch block without infarction. In this instance the ventricular gradient is exactly the same after as it was before the block Second, the T wave may be altered by any process, such as infarction or pericarditis, which delays regression locally. When both variables are operative, as in the case shown (Figure 33), a calculation of the magnitude and direction of the gradient, which is a vectorial sum of the mean manifest potentials of QRS and of T, may indicate by its abnormality that there is local injury grossly obscured by the bundle branch block

To return to the figure, it will be noted that the primary abnormality of the T wave is obscured whenever the area of the QRS deflections during block is large This amounts to saying that the secondary change in T wave is greater than the primary change Further, the effects of the infarct on QRS may be obscured by virtue of the fact that the mean direction of excitation of the septum, being from right to left in left bundle branch block, makes the left ventricular cavity positive Semi-

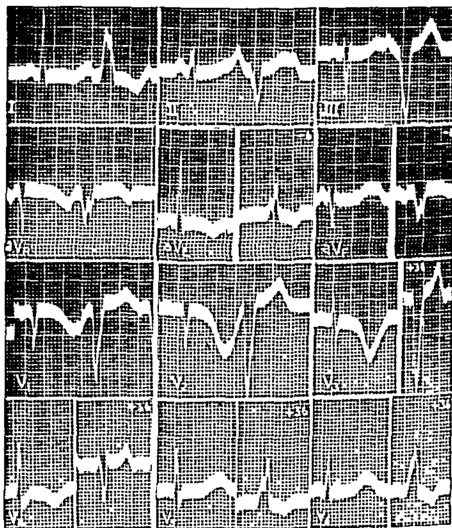


Figure 33. Myocardial infarction with intermittent left bundle branch block and complete and incomplete atrioventricular block. In the standard leads, and leads aVR, V_1, and V_6, adjacent complexes show the presence and absence of bundle branch block. In the other leads the two types were recorded at different times. The figures −6 and +36 mean that the record on which they appear was recorded 6 hours earlier or 36 hours later than the other in the same lead.

In adjacent complexes, supraventricular and aberrant, on the same strip, the area of QRST is approximately the same.

The figure illustrates the obscuration by left bundle branch block of the primary abnormalities of the T wave.

direct leads from the cavity will then be, at least partially, positive rather than negative as when intraventricular and septal conduction are normal This was not true in the present case because the infarct had caused little change in the supraventricular QRS.

Although a great deal of information is available on the ventricular gradient (40, 41, 42, 43), including its usual orientation in infarction and acute pericarditis (33), nevertheless it has not been used clinically except in a gross manner for the reason that it cannot be measured too accurately or easily (44). As soon as simpler instrumental means are available, it is probable that the measurement will be made routinely and will have considerable practical value.

A curious type of record has been encountered several times during cardiac catheterization. It is characterized by a large negative potential occurring toward the end of the T wave and extending well into the ordinarily isoelectric T-P interval (Figure 34) It has been observed to have a magnitude of as great as 8 0 mv, and its position in the ventricular electrocardiogram is about where the U wave would be expected. This negative potential may be on the basis of hyperpolarization (Figures 20 and 22E) brought about in some way by the pressure of the catheter-electrode on the endocardium of the right ventricle As can be seen in Figure 34, this potential is not reflected in a surface lead, varies in degree (lowest trace in figure), and disappears as soon as pressure of the electrode is released (end of top trace in figure). It is suspected that this type of injury may manifest itself clinically by modifications in the U wave which have heretofore been relatively neglected.

In summary, it may be concluded that experimental and clinical studies of the electrical behavior of injured ventricular muscle have shown a high degree of correlation, one with the other What minor discrepancies still exist, particularly between what is observed electrocardiographically and what is found anatomically, may be ascribed to the considerable disturbance in electrical behavior which occurs in the course of injury well in advance of anatomical changes which can be detected by present methods

Clinical Considerations of Pericardial Injury

It is generally agreed that the pericardium is a passive conductor. Electrocardiographic abnormalities which occur with disease of, or

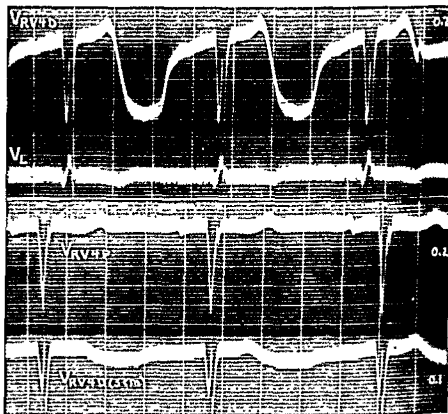


Figure 34 Intracardiac leads in a Negro male with unknown heart disease displaying a late, large, negative potential possibly caused by hyperpolarization (see Figure 22C). The upper record (V_{RV_4D}) from the right ventricle, made simultaneously with the potential of the left arm (V_L) shows a spontaneous disappearance of the potential at the end of the strip

The lower records were made with a double electrode catheter in the right ventricle with the electrodes 3 cm apart The proximal electrode recorded the probable true potential of the cavity (V_{RV_4P}), the distal electrode recorded the negative after-potential but in lesser degree than initially (V_{RV_4D}) To be noted is the occurrence of this potential near the end of the T wave and its persistence for almost 0.3 second into the T-P interval Time lines, 0 2 second, string sensitivity is normal unless otherwise indicated

trauma to, this membrane are ascribed to involvement of the subepicardial myocardium. An exception is the case of the massive pericardial effusion which theoretically causes some diminution in the size of *all* electrocardiographic deflections by virtue of its short-circuiting effect.

The changes which occur in the clinical electrocardiogram are well known (45). During the first week of an acute pericarditis, with the ex-

ception of uremic pericarditis, the S-T segment is characteristically elevated in leads I, II, V_L, and left-sided precordial leads, and depressed in leads V_R and V_1. Usually there is little or no deviation of the segment in lead V_F. During the inscription of the T wave the potential of the right arm and of the right sternal edge is negative, of the left arm and left leg variable, and of the precordial leads, other than V_1, positive and possibly notched. The spatial axis of injury is downward, forward, and to the left (Figure 30C).

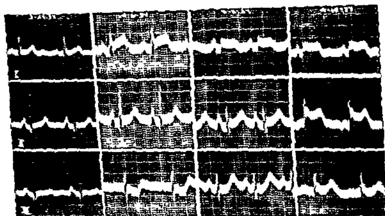


Figure 35. Standard leads before (3-29-39) myocardial infarction, after (4-6-39, 4-8-39) myocardial infarction, and after (4-10-39) development of fibrinopurulent streptococcus *pericarditis*. To be noted is the discordant displacement of the S-T segments in the second two curves and the concordant displacement of these segments in the last.

In a period of a few days up to several weeks there is gradual disappearance of the abnormal S-T segments, and reverse modifications in the T wave occur. In leads V_R and V_1 this deflection becomes positive, and in the standard leads and the leads from the left side of the precordium it becomes negative or less positive. In the leads from the left arm and the left leg the modifications are variable.

The characteristic concordant elevation of the S-T segments and subsequent concordant depression of the T waves in the standard leads are ascribed to involvement of the *subepicardial* myocardium around the apex dominantly on the anterior wall (Figure 30C). It hardly need be pointed out that pericarditis does not occur exclusively in this area, that

a similar electrocardiographic picture will be obtained if the lesion is diffuse, and that other abnormalities observed will depend on the orientation of the injured and ischemic myocardium to the surface electrodes. Further, pericarditis may exist without any electrocardiographic abnormalities.

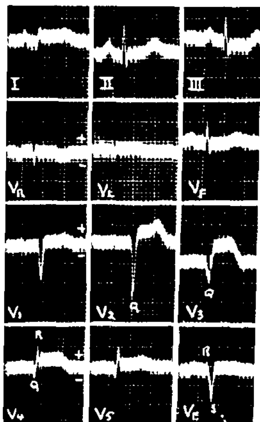


Figure 36 Standard leads (I, II, III), extremity potentials (VR, VL, VF), and precordial potentials (V_1 to V_6, and VE, tip of ensiform) in same patient as in Figure 35 recorded on 4-7-39. The changes are typical of transmural anteroseptal infarction with probable subendocardial involvement at the apex. Chest leads were recorded at 0.5N sensitivity of the string Time lines, 0 04 second

A problem of considerable practical interest is the differentiation of the electrocardiographic effects of pericarditis from those of myocardial infarction, especially since approximately 15 per cent of myocardial infarcts are complicated by a diffuse pericarditis (46). When the electrocardiograms are characteristic, the differential diagnosis is fairly easy, although exceptions occur particularly if the infarction is diffuse or if there are multiple infarcts. If in the course of myocardial infarction known to be elsewhere than at the apex a concordant displacement of the S-T segment occurs, almost certainly pericarditis is complicating the picture. The example (Figures 35 and 36) shows a control electrocardiogram (3-29-39) and two sets of standard leads (4-6-39 and 4-8-39) made after the clinical occurrence of myocardial infarction probably on 4-3-39. The precordial and extremity leads were made on 4-7-39 (Figure 36). The three latter records leave little doubt about the recent occurrence of

myocardial necrosis involving most probably the anterior wall of the left ventricle, and the adjacent anterior interventricular septum but not the apex (see leads V_4 and V_6). On 4-10-39, however, the standard leads display a new concordant deviation of the S-T segments, ascribed to a subepicardial myocarditis oriented in such a way as to yield an axis of injury directed downward and to the left. No pericardial friction rub was heard. Nevertheless this new finding suggested diffuse pericarditis, and the axis of injury indicated that the original infarction was not apical, or at least not transmural at the apex, for under such circumstances the subepicardial muscle would be dead, and the complicating pericarditis could not then have caused the direction that the new axis of injury took.

At necropsy there was a fresh occlusion of the anterior descending branch of the left coronary artery. The infarct was dominantly on the anterior wall of the left ventricle but did extend to the apex. In the latter region, however, the infarct was subendocardial only, and covered by a mural thrombus There was, in addition, a diffuse fibrinopurulent pericarditis which yielded on culture a hemolytic streptococcus. The probable portal of entry of this organism was in an area of freshly consolidated lung All subserous layers of the ventricular myocardium which were examined displayed a heavy infiltration with polymorphonuclear leukocytes

Even with infarction in other areas of the heart, the occurrence of concordant elevation of the S-T segments in the standard leads should excite suspicion of a complicating diffuse pericarditis. Although the diagnosis formerly was only of academic interest, in this era of potent antibiotics the recognition and energetic treatment of the purulent types may be lifesaving

From the discussion, it is apparent that an apical infarct can simulate, exaggerate, or nullify the electrocardiographic effects of a diffuse pericarditis depending on its intramural location (20) It also must be clear that the local pericarditis which occurs over a transmural infarct probably has no electrical effects because the muscle under it is necrotic and electrically inert

One possible manifestation of injury which has been observed in this laboratory to occur with unusual frequency in acute pericarditis is electrical alternans involving both QRS and T.

Summary

The several varieties of "injury" of the myocardium and pericardium which may be reflected in the electrocardiogram have been reviewed. An attempt has been made to demonstrate how an understanding of the membrane theory, coupled with a knowledge of the behavior of electrical currents in volume conductors, makes it possible to draw a conclusion in physiological terms and with a great deal of precision regarding the nature of the clinical disturbance which may be present. It is suggested that the era of describing, classifying, and cataloguing the nature and behavior of the action potential of the heart in a conducting medium is drawing to an end, and it is visualized that the future holds considerable promise for the exact correlation of the electrical with other functions of the myocardial cell.

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above the resting value, but is below the level that is reached by a normal heart. During sleep the cardiac output falls from a subnormal exercising level to a normal value for rest, and the output becomes sufficient for the resting needs, causing symptoms to disappear. As the heart becomes weaker, signs and symptoms of congestive failure persist at rest. In these patients the cardiac output is consistently below the resting value unless complicating physiologic or pathologic states are present.

Patients with advanced pulmonary disease, anemia, thyrotoxicosis, beriberi, and arteriovenous fistula have a high resting cardiac output. In them circulatory failure usually develops before the resting cardiac output falls below the value for normal subjects. The significant fact is the fall in cardiac output to a value below that found in the diseased state in the absence of heart failure

Stimuli which normally cause a rise in cardiac output frequently cause a fall in output in congestive failure. The reverse is also seen, and stimuli which cause a fall in the normal subject cause a rise in the patient with failure. Any stimulus, such as exercise or excitement, which normally increases the output may decrease the output in a fatigued heart. As fatigue increases, the ability of the heart to empty decreases. Anything which decreases the activity of the patient and normally decreases the output may increase the output of the fatigued heart

In uncomplicated heart failure which persists at rest, blood flow has been reduced in all areas where it has been studied (1). The reduction in splanchnic blood flow and cerebral blood flow is proportionate to the decrease in cardiac output, the reduction in renal blood flow is much greater Fasting splanchnic oxygen consumption is maintained at a normal level by widening of the arteriovenous oxygen difference. Cerebral oxygen consumption is usually normal but may be reduced slightly in severe failure. The reduction in blood flow to the various areas studied is related to the change in cardiac output and does not correlate with changes in venous pressure

Edema in heart failure may be divided into two types 1) that caused by a redistribution of fluid normally present in the body, 2) that caused by a gain in weight indicating an abnormal accumulation of salt and water. The first type, that produced by redistribution of normal fluid, is seen in pure form in patients who develop a massive infarct of the left ventricle without previous symptoms of heart failure (2) These patients

Chapter 12

EDEMA AND DYSPNEA OF HEART FAILURE*

Eugene A. Stead, Jr.†

THE CHIEF SYMPTOMS of congestive failure are weakness, swelling, and shortness of breath. All authors agree that weakness occurs because the heart cannot normally increase its output in response to the stimulus of exercise. There has been less general agreement as to the cause of the edema and dyspnea

The amount of blood pumped per minute in patients in heart failure is less than that pumped under similar conditions by patients without heart failure. The separation of patients with heart failure into two groups, those with high output failure and those with low output failure, has caused considerable confusion. The cardiac output at rest varies considerably from person to person. In the same patient it varies greatly in different physiologic and pathologic states. Exercise, eating, apprehension, and epinephrine increase the cardiac output; motionless standing decreases it. In a person with a normal heart the resting cardiac output will be decreased if the subject has myxedema, and increased if he has anemia, thyrotoxicosis, beriberi, or arteriovenous fistula. There are no absolute levels of the circulation above which circulatory failure does not occur and below which it always occurs The amount of blood pumped must be considered in terms of the immediate needs of the body rather than as an absolute value.

In the natural history of slowly progressive congestive heart failure it is the rule rather than the exception for symptoms to occur during periods when the cardiac output is above the resting level. Fatigue develops during the day when the subject is active The output is increased

* Presented October 12, 1951, at the 24th Graduate Fortnight of The New York Academy of Medicine.
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above the resting value, but is below the level that is reached by a normal heart. During sleep the cardiac output falls from a subnormal exercising level to a normal value for rest, and the output becomes sufficient for the resting needs, causing symptoms to disappear. As the heart becomes weaker, signs and symptoms of congestive failure persist at rest. In these patients the cardiac output is consistently below the resting value unless complicating physiologic or pathologic states are present.

Patients with advanced pulmonary disease, anemia, thyrotoxicosis, beriberi, and arteriovenous fistula have a high resting cardiac output. In them circulatory failure usually develops before the resting cardiac output falls below the value for normal subjects. The significant fact is the fall in cardiac output to a value below that found in the diseased state in the absence of heart failure.

Stimuli which normally cause a rise in cardiac output *frequently cause* a fall in output in congestive failure. The reverse is also seen, and stimuli which cause a fall in the normal subject cause a rise in the patient with failure. Any stimulus, such as exercise or excitement, which normally increases the output may decrease the output in a fatigued heart. As fatigue increases, the ability of the heart to empty decreases. Anything which decreases the activity of the patient and normally decreases the output may increase the output of the fatigued heart.

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may rapidly develop massive pulmonary edema. Blood is pumped into the lungs by the right ventricle, and it is not removed by the left ventricle. The pulmonary capillary pressure rises sharply, and fluid is pushed into the lungs. Fluid enters the blood stream from the extracellular areas supplied by the systemic circulation, and thus becomes available for increasing the pulmonary edema. The hematocrit reading and plasma protein concentration indicate a slight to moderate fall in blood volume. The weight of the patient is unchanged.

In the second type of edema, fluid is retained in the body and weight gain occurs. For some reason related to heart failure, the kidneys are excreting less water than the patient is drinking The exact reason why the kidneys retain fluid has not been agreed upon.

In chronic heart failure there is a striking disturbance in the circulation to the kidney. The renal blood flow is reduced to a value only one-third to one-fifth that of normal, and the glomerular filtration rate is reduced to a value one-half to one-third of normal (3). This reduction in renal blood flow and filtration rate is related to the level of cardiac output, but shows no obvious correlation with the level of venous pressure. Tubular function remains good. The author believes that this reduction in filtration rate, secondary to the reduced renal blood flow in the presence of relatively well-functioning tubules, is the primary cause of the edema in congestive failure. According to this theory, the normal tubules are unable to depress their sodium reabsorbing function enough to allow the escape of large quantities of sodium in the urine when the amount of sodium presented to them is reduced to the degree seen in heart failure. This thesis emphasizes that the reabsorptive ability of the tubules in both normal subjects and patients with heart failure can be altered by various agents acting on the tubule, but it emphasizes also that the amount of sodium retention produced by these factors acting on the tubules is influenced in a quantitative rather than a qualitative way by the reduced filtration rate In other words, both normal subjects and patients with heart failure retain sodium during light exercise, but the amount of sodium retained by the cardiac exceeds that retained by the normal subject. This quantitative difference is believed to be the result of the low filtration rate in the presence of reasonably well-functioning tubules.

Other investigators believe that the retention of salt and water is

caused by a rise in renal venous pressure. Still others feel that a rise in systemic venous pressure causes loss of fluid into the tissue and that this loss of fluid from the blood stream in some way causes retention of fluid by the kidney. Many other persons think that the circulatory disturbance in the kidney is not very important, and that the sodium retention of heart failure is caused by the action of various hormones on the renal tubules. There is evidence that urinary corticoid excretion is increased in heart failure.

Our chief difficulty in settling the question of edema in heart failure lies in our ignorance of the factors which control sodium excretion in normal subjects. We know that sodium excretion is increased on a high sodium intake and lowered on a decreased sodium intake More sodium is excreted during the day than during the night Lowering the blood volume by bleeding and motionless standing increases sodium retention. Cortisone and desoxycorticosterone cause sodium retention. Whether these hormones are important in the hourly and daily variations in excretion of sodium in normal subjects is not known.

In this discussion we have blithely assumed that the primary cause of cardiac edema is sodium retention and that retention of water and chloride are secondary phenomena. This is based on the clinical observations that 1) the sodium ion when given as bicarbonate, lactate, or chloride increases edema formation; 2) chloride ion when given as calcium chloride or ammonium chloride does not increase edema, and 3) when sodium is rigidly restricted, patients with heart failure excrete water relatively well. In patients with sudden heart failure the concentrations of sodium and chloride in the plasma are normal. In many patients with chronic failure the sodium and chloride concentrations in the plasma are low. This has led many people to wonder if too much emphasis is not put on sodium retention, and they raise the question of whether in certain instances water retention may not be the primary defect (4) Let us consider what we know about low sodium concentrations in the serum and about the regulation of water metabolism.

Data collected in many laboratories have shown a surprising number of patients with occurrence of low sodium and chloride concentrations in the plasma (4, 5, 6). In any chronic illness, with or without edema, we are apt to find the plasma sodium below 120 mEq Many of these patients have none of the signs of circulatory difficulty of the type we are

accustomed to see in patients in Addisonian crisis. Indeed, we may well blame our friends in endocrinology for making us believe that patients always appear acutely ill when the sodium concentration becomes low. We forgot that the Addisonian appears very ill not because the electrolytes are out of balance but primarily because his entire body homeostasis is upset by the lack of a functioning adrenal cortex.

These data indicate that, in such chronic illnesses, the osmotic activity of the cells is decreased. In the past we have been taught that cellular osmolarity is rigidly defended, but the finding of low electrolyte concentrations in the plasma can only mean that the osmotic activity of the cell is also low Cellular osmolarity can also increase as shown by *observations after electric shock therapy* (7). *These data are compatible* with 1) retention of an abnormal quantity of water because of a disturbance in the mechanisms controlling water secretion, with subsequent dilatation of electrolytes; 2) lowering of osmotic activity of the cells so that water is retained by normal rather than abnormal function of the water-regulating mechanism. Any fluid-regulating mechanism which was set to fluctuate around the osmotic pressure of cells would not give an invariable level of electrolyte activity in the plasma, but would regulate the plasma to correspond to the variable osmotic activity of the cell. This has been suggested by Welt et al. as a possible explanation for certain hyponatremic states (7).

When a normal person drinks a large quantity of water, the level of electrolytes in the blood and extracellular fluid is lowered. The water passes into the cells to restore the osmotic equilibrium between intra- and extracellular fluid. This fall in electrolyte concentration acts on osmoreceptors in the area supplied by the internal carotid artery and causes an inhibition of *secretion of the antidiuretic hormone* of the posterior pituitary gland (ADH). When the renal tubules escape from the action of ADH, absorption of water in the distal tubules is decreased and water diuresis occurs If hypertonic saline is now injected intravenously, the electrolyte activity of the blood and extracellular fluid is increased and water passes out of the cells to restore osmotic equilibrium. Immediately the osmoreceptors respond to the cellular dehydration with stimulation of the postpituitary gland to produce ADH. Tubular reabsorption of water in the distal tubule is increased, and the water diuresis is checked.

If ADH is supplied exogenously by giving Pitressin repeatedly in small doses, water drinking results in a considerable increase in intra- and extracellular water, and the sodium and chloride concentrations in the plasma are considerably decreased. May not such a mechanism be the cause of edema in patients with heart failure and low concentrations of chloride and sodium? May not the water retention itself result in a secondary retention of sodium and chloride? *We do not think so*, because the administration of Pitressin to normal subjects over a 24-hour period does not cause the characteristic retention of sodium, so typical of heart failure. Water is retained, but not the salt (8).

Let us consider more closely the findings in chronic illness with low sodium and chloride concentrations. The patients do not show signs of peripheral circulatory failure. If sodium chloride intake is increased, either edema occurs because of expansion of the extracellular fluid volume or the salt is excreted in the urine. In either instance the concentrations of sodium chloride may change little. If salt is restricted in the diet, the excretion in the urine becomes greatly reduced and the fall in concentration in the plasma is slowed down. If desoxycorticosterone or ACTH is given salt retention occurs, but this results in an expansion of extracellular fluid and not in a rise in concentration in the plasma. If water is given a diuresis occurs. If hypertonic salt is given intravenously the diuresis is broken. We thus have evidence of a new level around which function the osmoreceptors regulating pituitary ADH secretion function. These observations suggest that in chronic illness cellular osmolarity changes and, therefore, the concentration of electrolytes in extracellular fluids is altered. Water is not retained to dilute the electrolytes because of the overactivity of postpituitary ADH. The pituitary mechanism functions normally, but it is working around a new osmotic setup.

We believe, then, that we have three common situations in which the serum sodium and chloride fall to low levels. Water intoxication is a fourth and rare cause. The most common situation is the one resulting from changes in cellular osmolarity. Administration of salt can only expand the volume of extracellular water. It cannot raise the concentration in extracellular water because this would cause cellular dehydration.

Less common is the acutely occurring low salt syndrome in which the concentration of sodium and chloride is low because of constant loss

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is of normal tonicity as long as cell tonicity is normal, but will change as cellular tonicity changes.

The third great symptom of cardiac failure is dyspnea. The basis for cardiac dyspnea is the structural changes which occur in the lung as a result of heart failure. Characteristically, the left heart is more damaged than the right and blood accumulates in the lungs. The pulmonary capillary pressure rises. Early in the course of heart failure, any fluid retained in the body by the kidneys tends to be dumped preferentially in the lungs. This tendency may become less marked as advanced heart failure occurs, and both ventricles fail equally.

When the patient with congestive failure is dyspneic at rest, he is pumping more air in and out of his lungs than do normal subjects. His dyspnea is a combination of decreased breathing space and increased ventilation. The cause of the increase in volume of air respired has never been fully determined.

The overbreathing causes a fall in the carbon dioxide content of the arterial blood and serves to maintain oxygenation of the arterial blood. The fact that the increased breathing is essential to maintaining full oxygenation is easily demonstrated by the use of morphine. As the ventilation is brought to a normal level by the action of morphine, the arterial oxygen content decreases to a point well below the normal level.

It has been stated repeatedly that in many patients with dyspnea from heart failure, the arterial oxygen saturation is normal and that a need for oxygen is not the stimulus for increased ventilation. It is true that the cardiac patient has nearly normal saturation and that the slight fall in arterial oxygen saturation characteristic of the cardiac has no easily detectable effect on the breathing of a resting normal subject. But can these data from the resting normal be applied to the dyspneic cardiac?

We know that a normal subject at rest can breathe 100 per cent oxygen with little effect on his breathing. If he is doing heavy exercise, however, breathing 100 per cent oxygen causes a sharp fall in ventilation. Will the cardiac patient's response to changes in oxygen tension be like that of the man at rest or like that of the exercising man?

Data collected by Hickam (9) show that the orthopneic cardiac has a sharp fall in ventilation when he breathes 100 per cent oxygen, and that this fall is much greater than will occur in normal resting subjects with

of sodium chloride from the body either from the gastrointestinal tract or through kidneys whose tubules are injured by disease or temporarily paralyzed by the influence of mercurial diuretic. The acute renal low sodium syndrome has the following characteristics: on a low sodium chloride intake, the loss in the urine is greater than the intake of salt. Regardless of the level in the plasma, this loss continues, and does not stop until death or anuria occurs. It cannot be prevented by the use of desoxycorticosterone or ACTH. It is eventually associated with peripheral circulatory failure. Giving hypertonic sodium chloride solution results in dramatic clinical improvement.

The third common low sodium syndrome is a combination of low cellular osmolarity and excessive loss of sodium from the body. Let us consider an example. A patient with chronic illness has been placed on a low sodium intake. After a time he does not do well; the sodium concentration is determined and found to be very low. He is given a little sodium chloride intravenously with dramatic improvement. Repeat laboratory examination shows that the sodium has risen only a little and is still much below the normal value. More sodium is given. The patient does not improve further; the extracellular volume rises and clinical edema occurs. If one insists on treating such a patient until the sodium concentration returns to normal, death frequently occurs from drowning.

A fourth, but less common, cause of low sodium syndrome is the fall in electrolytes produced by water intoxication. In postoperative patients who receive only glucose and water and who have lost some salt by sweating, a syndrome characterized by confusion, rise in blood pressure, and reduced urine output may occur. Sodium, potassium, and chloride concentrations in the plasma are low. Hypertonic salt solution given intravenously results in dramatic improvement. These same findings are seen in patients with Addison's disease who are being treated with desoxycorticosterone. If they force water, stop eating, and discontinue their extra salt, the syndrome of water intoxication develops. In severe congestive failure where marked discomfort is present, or where infection or pulmonary infarction has occurred, one may retain water because of the repetitive neurogenic discharge of postpituitary ADH. Hypertonic saline in these patients usually aggravates the edema.

So much for generalized edema. The cardiac retains salt and water because the kidneys do not excrete sodium normally. The retained fluid

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a corresponding change in oxygen tension. The cardiac who is dyspneic at rest responds to minor changes in oxygen tension in a way similar to that of a normal subject doing heavy exercise. The mechanism for this increased sensitization to oxygen remains to be determined.

Cheyne-Stokes respiration is one of the dramatic clinical findings in patients with heart failure.

Pryor (10) has recently described one of the mechanisms responsible for this type of breathing. These patients have large hearts and a long circulation time. The irregularity in breathing occurs without any evidence of disturbance in the carotid sinus or respiratory centers. The breathing follows closely the changes in arterial blood gases, and their response to a given change in arterial blood is a normal one. Coordination between the lungs and the medulla is lost because of the large sac of blood placed in the heart between the lungs and the medulla. Overbreathing does not affect the medulla until the entire heart is filled with aerated blood. When this red, overventilated blood reaches the medulla, apnea occurs. The blood entering the left side of the heart becomes venous as it perfuses through the motionless lungs, but the blood leaving the heart remains arterial until the entire dilated heart is filled with venous blood. When venous blood finally reaches the medulla, marked overbreathing occurs, but this can have no effect on the respiratory centers until the venous blood empties out of the heart. This is only one of the mechanisms for Cheyne-Stokes breathing.

The tools for a study of respiratory stimulation in various disease states are now available, and during the next few years our knowledge of the mechanisms of dyspnea is certain to be greatly increased.

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of both forms of therapy now permit far better control of peripheral circulatory failure than ever before. Shorr's investigations of the epinephrine antagonists have not yet led to specific therapy for the loss of tone in arterioles and precapillary sphincters due to high levels of vasodepressor material of hepatic origin, although this type of shock has been corrected by dialysis of the blood in the artificial kidney.

Circulatory failure of the acute peripheral type is compensated for by the body, as we may see after hemorrhage, by rise in venomotor and arteriolar tone, and by conservation of sodium chloride and water. The latter, effected by endocrine control of the kidney, permits restoration of blood volume and tissue turgor. Also there is a new formation of plasma protein and of red cells, so that the blood lost is soon fully replaced Cardiac output falls when we are in the sitting or erect posture, and in studies of patients with postural hypotension, whose beds are tilted so the shoulders are well above the legs throughout both day and night, a rise of several hundred cubic centimeters in blood volume occurs in a week or two (1) The body brings into play all these restorative reflexes, whether circulatory failure is due to hemorrhage, posture, or to any other cause.

In peripheral failure cardiac output falls because venous return and ventricular filling are inadequate When the pericardial sac is distended with fluid, or the pericardium scarred and drawn tight around the ventricles, heart failure is due largely to inadequate diastolic filling of the ventricles These conditions usually develop slowly, and as the compensatory reflexes come into play, there is a rise in blood volume and in body water far above the normal level. Combined with the rise in tone of venules, this raises pressure in the auricles, but does little to improve ventricular filling when there is high resistance due to pericardial disease

These forms of circulatory failure might be considered as preventricular, in analogy with prerenal uremia or edema, while the common form of circulatory failure, congestive heart failure, is in most instances ventricular or myocardial. The fundamental problem of myocardial failure is one with which only those who have Professor Szent-Gyorgyi's experience and imagination can deal It is the problem of muscular fatigue in the special biochemical setting of the heart muscle, fatigue in a muscle which must contract at least thirty times a minute to main-

Chapter 13

THE MECHANISM AND MANAGEMENT OF CIRCULATORY FAILURE*

William Dock †

CIRCULATORY FAILURE exists when any tissue, or the body as a whole, receives less than an optimal blood flow. Often the failure is local, as when the retina receives inadequate blood in a pilot pulling his airplane out of a dive, or when the myocardium is poorly perfused because of coronary sclerosis. General failure occurs when the minute volume flow of blood into the aorta fails to meet the needs of the whole body. This happens in all of us on exertion, and leads to oxygen debts of varying magnitude. Such deficits in flow are made up after exertion ceases. Acute failure also occurs after severe hemorrhage, or with venous pooling due to reclining at a 75° angle on a tilt table, or after taking nitrites while quiet and erect. In all these conditions the roentgen shadow of the heart decreases, the rate becomes rapid, and blood pressure is normal or low. As the systolic pressure falls toward or below 90 mm Hg, and the patient develops nausea and apathy, circulatory failure progresses into shock. This can occur from dehydration, adrenal insufficiency, or hepatic necrosis, as well as from trauma and hemorrhage.

Peripheral circulatory failure may be due entirely to decrease in blood volume, or, as in spinal cord lesions, entirely to loss of vasomotor and venomotor tone. In many acute infections and intoxications, both factors are present. Restoration of blood volume by transfusion will not completely relieve the disorder if venomotor and vasomotor tone are lost, nor will restoration of vascular tone, by norepinephrine infusion, give complete relief if blood volume is greatly reduced. Combinations

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in the circulation. When thiamine deficit sets in, additional cardiac output is needed Pyruvate seems to act as a vasodilator and keeps the vascular bed open even when all other needs have been met. In cirrhosis of the liver, open shunts in the skin and elsewhere may double blood flow in relation to normal basal needs Failure to meet all such excessive demands may lead to severe symptoms of heart failure at cardiac outputs far above normal. This is similar to uremia in a patient with two or three times the normal daily output of nitrogenous metabolites, due to high protein intake or rapid breakdown of body protein

It might be thought that such increases in demand for blood flow would be important direct causes of heart failure Actually the cost to the heart muscle of increasing stroke volume when the peripheral resistance falls is remarkably small During exercise in normal people stroke volume rises but heart volume falls. Since oxygen use by the heart varies with heart volume (3), the fall in resistance must more than compensate for the rise in stroke volume, which can thus be maintained at reduced levels of oxygen use per beat. We may conclude that the burden on the heart, due to increased volume flow of blood, is usually less than one would think from the rise in pulse rate. Such acceleration regularly occurs with increase in venous return

Arterial hypertension, whether systemic or pulmonic, also adds to the burden of the ventricle, but we have no way to measure how much. Systemic pressure may gradually double, and pulmonic pressure rise four- or fivefold yet heart failure may not set in, and ventricular volume increases far less than one would calculate from Starling's curves relating cardiac work to cardiac volume (4). The curves deal with acute situations, and with an acute rise of pressure, heart failure may occur as would be predicted In chronic disease, the muscle cells become thick, not long, and the work is done very efficiently In such patients, rise in rate, not the level of pressure, is the best clue to the cardiac burden per gram of muscle Even in acute experiments, doubling the systemic pressure level increases work per gram of muscle only 25 to 30 per cent

Doubling the rate imposes on the heart, beating at constant volume, an increase in oxygen need of only 50 per cent per minute, and reduces oxygen used per beat (4). But rise in rate also shortens the time available for restoration of the molecular arrangements and high energy chemical

tain our vital functions. Why do hearts carry their heavy burdens for decades, and fail even when less is demanded of them in senescence, and why is this sort of failure reversed, to some degree, by digitalis glucosides? These are the problems now being attacked by the biochemist. It is simple enough for the clinician to explain to himself the failure of a muscle inflamed by myocarditis, or of myocardial cells filled with glycogen or buried in amyloid. Since none of these simple causes are present in most cases of heart failure at ages over 40, the clinician seeks an explanation from the biochemists, whose progress is most exciting, even though we catch only fleeting glimpses through our fog of ignorance.

In chronic cardiac failure—failure of the ventricles to expel in systole the blood which overfills them in diastole—all of the compensatory mechanisms seen after hemorrhage are at work, and the patient has a high blood volume, excessive extracellular fluid, and yet continues to retain sodium and water (2). If depleted of sodium, his renal function may fail and his plasma sodium fall to critical levels, because he still retains water in excess of his osmotic needs. These results of the body's compensation for inadequate output of blood cause most of the symptoms of heart failure, and will be considered in detail by other speakers But it must be emphasized that the rate at which symptoms increase and the severity of the symptoms observed do not give a valid index of ventricular fatigue, but are usually functions of the excess of the patient's salt intake over the normal needs of the mammalian body. The latter, for sedentary people in temperate climates, does not exceed 200 mg of sodium per day, while American diets provide 3000 to 8000 mg a day. This excess makes rapid accumulation of edema easy, even with mild degrees of ventricular failure which would not be apparent with physiologic levels of sodium ingestion

The physician is chiefly concerned with congestive failure occurring in middle age, in sedentary people, with the usual excessive salt intake. Symptoms develop rapidly in such patients whenever cardiac output falls a little below optimal needs of the body and when salt ingestion suddenly rises. The optimal needs for flow include not only the blood to keep oxygen tension at proper levels in all organs and replace oxygen debts due to exertion, but blood to maintain normal flow to the renal filter, to the dermal heat-radiating system, and to any leaks or shunts

in the circulation When thiamine deficit sets in, additional cardiac output is needed. Pyruvate seems to act as a vasodilator and keeps the vascular bed open even when all other needs have been met. In cirrhosis of the liver, open shunts in the skin and elsewhere may double blood flow in relation to normal basal needs. Failure to meet all such excessive demands may lead to severe symptoms of heart failure at cardiac outputs far above normal. This is similar to uremia in a patient with two or three times the normal daily output of nitrogenous metabolites, due to high protein intake or rapid breakdown of body protein.

It *might* be thought that such increases in demand for blood flow would be *important* direct causes of heart failure. Actually the cost to the heart muscle of increasing stroke volume when the peripheral resistance falls is remarkably small. During exercise *in normal* people stroke volume rises but heart volume falls. Since oxygen use by the heart varies with heart volume (3), the fall in resistance must more than compensate for the rise in stroke volume, which can thus be maintained at reduced levels of oxygen use per beat. We may conclude that the burden on the heart, due to increased volume flow of blood, is usually less than one would think from the rise in pulse rate. Such acceleration regularly occurs with increase in venous return.

Arterial hypertension, whether systemic or pulmonic, also adds to the burden of the ventricle, but we have no way to measure how much. Systemic pressure may gradually double, and pulmonic pressure rise four- or fivefold yet heart failure may not set in, and ventricular volume increases far less than one would calculate from Starling's curves relating cardiac work to cardiac volume (4). The curves deal with acute situations, and with an acute rise of pressure, heart failure may occur as would be predicted In chronic disease, the muscle cells become thick, not long, and the work is done very efficiently. In such patients, rise in rate, not the level of *pressure*, is the best clue to the cardiac burden per gram of muscle Even in acute experiments, doubling the systemic pressure level increases work per gram of muscle only 25 to 30 per cent.

Doubling the rate imposes on the heart, beating at constant volume, an increase in oxygen need of only 50 per cent per minute, and reduces oxygen used per beat (4). But rise in rate also shortens the time available for restoration of the molecular arrangements and high energy chemical

bonds needed for contraction. The evidence from clinical experience points to slowing down of these chemical reactions in myocarditis and in the aging heart, thus making the ventricles especially prone to fatigue or partial exhaustion of contractile force if driven at rapid rates. While elderly patients with complete heart block may have low minute volume flow, and are unable to increase this much on exertion, they do maintain high stroke volumes against normal or high arterial resistance, and rarely show classical evidence of congestive failure. Even when they have had previous myocardial infarction and have bundle branch block, they usually have large ballistocardiographic waves of normal contour. This indicates vigorous ejection of a large stroke volume by the slowly beating heart.

At the opposite extreme we see that when young people with normal hearts have an attack of paroxysmal tachycardia, heart failure develops in a day or two. In the first hours, the heart is small, as seen by x-ray, just as with the tachycardia of exercise, but it gradually dilates as it becomes fatigued by sustained rates over 180 per minute, and in one or two days, venous pressure rises, rales develop in the lungs, and the liver becomes swollen and tender. With termination of the rapid rate, everything returns to normal in a few days There can be no doubt in the minds of those who study cases of block on one hand and of tachycardia on the other that that acceleration of the heart is the most potent factor in causing heart failure Because increase in minute volume flow is regularly associated with acceleration in rate, it too has a causative role far greater than would be the case if stroke volume alone were increased. Cardiac acceleration is a common sequel of anger, apprehension, and related moods, so that heart failure may be precipitated by emotional storms, just as it is by fever and by other conditions, such as beriberi, hyperthyroidism or cirrhosis, which accelerate the pulse As the average age group of patients increases, heart failure occurs more often as a result of a given degree of acceleration, or of change in stroke and resistance. Also, acceleration causes failure to develop more quickly in older people, and the rise in rate required to cause failure becomes less marked. At age twenty-five, heart failure does not occur in normal hearts driven less than 150 per minute, at ages over fifty it often occurs at rates of only 100 to 120, and disappears when the rate falls below 80.

It was long taught that failure of the coronary bed to grow, and

inability of oxygen to diffuse into thick fibers, could explain myocardial failure in hypertrophied but otherwise presumably normal ventricles. Bing and Goodale (5) have shown that flow is normal and oxygen uptake is high in hypertrophied hearts without coronary sclerosis, and it is now realized that oxidation can occur by electron transfer along long molecules so that the calculations on diffusion into fibers have become less significant (6) Today we can assume that chronic heart failure due to anoxia occurs only with coronary occlusion or with anemia of extreme severity. Acute anoxia due to ischemia or anemia can develop swiftly in shock and hemorrhage, and may precipitate failure of the myocardium and acute pulmonary edema But, in striking contrast to these types of failure is the extreme infrequency of chronic myocardial failure with congestive phenomena in younger subjects with fatal coronary sclerosis This was evident in the hundreds of soldiers under thirty-five years of age, whose deaths were studied at the Army Institute of Pathology (7), and also in young civilians (8) Even with myocardial necrosis and ischemia, heart failure is most *uncommon* before the age of forty. In the light of our present knowledge, myocardial *necrosis* and scarring, and coronary insufficiency, contribute to the work of the ventricles, cause pain, cardiac irregularities, and tachycardia due to apprehension, but coronary insufficiency or failure of the *coronary bed* to hypertrophy are not the direct causes of the fatigability of the ventricular muscle which underlies *myocardial* failure. Pain, not fatigue, is the result of ischemia in voluntary and in cardiac muscles

The failure of a heart which has lost myocardial efficiency or the ability to restore its molecular machinery rapidly after each beat is therefore hastened more by acceleration than by other factors, while the rate of evolution of symptoms depends largely on the daily intake of sodium. Symptoms also are aggravated by other stimuli to salt retention, the most common being operative shock and premenstrual steroid stimulation of renal reabsorption of sodium The most readily demonstrable and easily corrected cause of myocardial fatigability are abnormal levels of plasma potassium and a deficiency of water-soluble vitamins, specifically thiamine. All the other causes are vague and hypothetical, but some of them may be corrected, in part, by digitalis. The cardiac glucosides may also reverse the ill effects on the heart of high or low potassium levels, and of excessive dosage of desoxycorticosterone.

From this schematic description of heart failure, the general principles of therapy are obvious. Therapy is most successfully directed at the phenomena due to attempted restoration of optimal output—that is, the increase in blood volume and the retention of sodium. Bleeding, when hemoglobin levels are over 12 gm per cent, the liver large, and the neck veins full, not only relieves the engorged venous system but may actually lead to a rise in cardiac output, by relieving overdilation and tachycardia. Sodium depletion, by diet, mercury, and cationic exchange resins, not only relieves pulmonary edema but by reducing myocardial edema may improve the function of the ventricles. Thus, therapy directed at secondary phenomena which cause distress may actually improve cardiac function

Slowing the heart is of utmost importance, and this may occur merely through relief of fright, when the patient has confidence that the doctor is competent and diligent. This deceleration is further helped by judicious use of a narcotic for a day or so, and sedation thereafter. It may be greatly assisted by a cool oxygen tent, if the patient is not alarmed or annoyed by this device. A decrease in symptoms is often effected by proper posture alone Often in urgent dyspnea the most restful posture is sitting in the armchair before a table piled with pillows on which the patient can lean forward In some cases an ordinary bed, with the head end tilted up so the whole bed is at 30°, is more comfortable than the propped-up Gatch bed On a tilted bed the patient can roll on his side, or lie prone.

Digitalis is of greatest value when it slows the ventricles in auricular fibrillation, but it may have striking effects on failure with regular rhythm When given with mercury, diet, sedation, etc, its value cannot be assayed, when given after some days on a constant regime it causes no striking benefit in more than half these cases, but in about one-third of the older patients, and occasionally even in children, it clearly is responsible for great improvement in myocardial vigor and relief of symptoms. It should always be given until it gives a good result, or causes coupled rhythm, nausea, or other toxic signs These latter may be caused by half the average digitalizing dose (1.5 mg digitoxin, 1.5 gm folia, 0.6 mg ouabain), or may not occur until twice this dose has been given within 36 hours for digitalis or 6 hours for strophanthin. Perhaps the highest praise a doctor can hope to deserve is the remark

my father made of a colleague he greatly admired. "He knows how to use digitalis."

Correction of anemia is an urgent matter in some patients with heart failure and can safely be done with packed red cells. Starvation, disguised as Karrell diet, is usually wrong, although weight reduction is frequently necessary as a long-term project. The cardiac needs a simple solid diet, with small frequent feedings and minimal salt intake as long as blood urea is below 80 mg per cent. Five milligrams a day of thiamine is adequate for correction of beriberi heart disease, and is a simple supplement needed by many cardiacs, so that we use it routinely. If there is good reason to suspect Graves' disease, suitable tests and antithyroid therapy should be undertaken at once. Creatinuria and basal metabolism do not fall in the first few days of therapy, but radioactive isotope studies and protein-bound iodine determination should not be deferred until after therapy is started. All tests are more satisfactory if completed before antithyroid drugs are given. It may, however, be unwise to defer therapy in some cases where the diagnosis is strongly suspected and heart failure is not easily brought under control.

The management of heart failure, which so often begins as an emergency, usually develops into a permanent way of life. In the future, surgery will be more often undertaken to lessen the load on the heart and hypothyroidism will eventually be induced in cases not otherwise held in check. The fundamental elements for effective control of heart failure are a hopeful, well-instructed patient and a physician who appreciates the hazards of overcautious regimes, the value of maintaining good morale and bodily fitness, and the need for exhausting simple and reversible forms of therapy before considering those which are costly, hazardous, and irreversible.

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Chapter 14

THE TREATMENT OF SOME BACTERIAL INFECTIONS OF THE HEART AND PERICARDIUM*

Thomas H. Hunter†

PURULENT PERICARDITIS is rapidly becoming a medical curiosity. Infections of the pericardium by pyogenic organisms used to be a fairly common accompaniment of severe uncontrolled infections such as pneumococcus pneumonia, staphylococcus septicemia, meningococcemia, and the like. With the modern antibiotic armamentarium at hand patients rarely progress to the stage of sepsis where this complication arises. It is interesting that in reviewing the literature for the past five years I was unable to find a single article in English devoted to the subject, and for this reason as well as because of my own lack of first-hand experience in treating patients with purulent pericarditis, I should like to limit my remarks to a few general suggestions.

The therapeutic problem appears to be analogous to that in empyema with the additional hazards of cardiac tamponade and the later development of constrictive pericarditis. The first point of similarity is that the diagnosis can only be made with a needle. Secondly, as in empyema, systemic antibiotics alone cannot be counted on to handle purulent pericarditis. Local instillation of appropriate antibiotics is indicated since diffusion of adequate concentrations from the blood stream into serous cavities is problematical. Actually there are no adequate data that I know of on the levels of antibiotics in pericardial fluid after parenteral administration.

Should signs of uncontrolled infection or persistent cardiac compres-

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The antibiotics used were generously supplied by Charles Pfizer and Co., and penicillinase by Schenley Laboratories, Inc.

sion continue in spite of repeated paracenteses, the presence of loculation with the formation of adhesions between the parietal and visceral layers of the pericardium must be suspected and appropriate measures instituted The choice lies between surgical drainage and "medical debridement" with enzymes. Although I would hesitate to recommend it as an established procedure, the use of streptokinase and streptodornase would seem logical as a less drastic measure to be tried before resorting to surgery. These enzymes were instilled in the pericardium of one patient in Barnes Hospital this year without serious untoward effects.

The remaining time will be devoted to a discussion of some aspects of the treatment of bacterial endocarditis, which is still by far the most important bacterial infection involving the cardiac structures both in terms of frequency of occurrence and gravity of prognosis. During the past decade, it is true, the outlook in this disease has been transformed from one of utter hopelessness to one in which cure is to be expected as the general rule. Recently there has been a tendency on the part of some physicians to consider the subject a closed book, and to think that all one has to do in treating the infection is give several million units of penicillin a day for a few weeks. While such an attitude is understandable, it is also somewhat dangerous when one remembers that the mortality in bacterial endocarditis still averages around 30 per cent and has not been reduced appreciably in the past five years in spite of the appearance of several new antibiotics on the market during that time. Furthermore I cannot help being somewhat alarmed by the fact that three of the last four patients I have seen with the disease have had infections caused by an enterococcus. During the past year and a half only five patients harboring penicillin-sensitive streptococci have come under my care. I am sure that my experience does not reflect the true incidence of penicillin-resistant infections, but there is other evidence that resistant nonhemolytic streptococci are probably on the increase and account for somewhere around 20 per cent of cases (1) now rather than the 4 or 5 per cent encountered six years ago The situation with staphylococcal infections is even worse in that two-thirds of the strains isolated from a recently published series of cases (1) were found to be resistant to penicillin.

These facts make it clear that now more than ever before rule-of-thumb therapy with penicillin alone is hazardous and that every reason-

able effort should be made to establish an etiologic diagnosis together with a careful evaluation of the infecting organism as to its resistance or sensitivity to the available antibiotics

This leads us to the next real reason for discussing bacterial endocarditis at this time How is one to decide which antimicrobial agent, or what combination of them, to use in a given situation?

With this problem in mind I should like to turn to a consideration of some of the fundamental mechanisms which seem to be involved in the cure of this disease, and to review some experimental work designed to have bearing on the therapy of this infection

Bacterial endocarditis presents, I think, a rather special therapeutic problem which sets it apart from many of the other bacterial infections of man, in that it seems to be necessary with chemotherapeutic agents to eradicate the last viable organisms from the vegetations without expecting much help from the natural and acquired defense mechanisms of the host Of course the latter are important in the recovery of the patient and in holding the infection in check, but by themselves they almost never succeed in completely eliminating the bacteria.

Furthermore I think it is safe to say that clinical experience to date suggests strongly that administration of a bacteriostatic drug even for many weeks is usually not successful Specifically the sulfonamides, aureomycin, chloramphenicol, and terramycin are all primarily bacteriostatic for the nonhemolytic streptococci and all have been disappointing in the treatment of bacterial endocarditis (2, 3, 4, 5, 6, 7, 8, 9, 10) although the data on the last two are still scanty

In contrast to the usual sensitivity tests which measure only the concentration of antibiotics necessary to produce inhibition of the growth of a small inoculum of organisms, generally under optimal conditions for the action of antibiotics, the studies reported here are designed to test antibiotics under conditions less favorable to their action

The typical in vitro responses of the enterococci to various antibiotics are seen in Figures 37–41. In these figures, as in subsequent ones to be shown, are plotted the results of some experiments which were carried out as follows A large inoculum of an overnight culture of the organism to be studied was added to a series of flasks containing 50 ml of nutrient broth so that a final concentration of between 10 and 100 million viable organisms per milliliter was obtained. Antibiotics were added at the time

of inoculation to all flasks except the control to give the concentrations noted on the charts. At various intervals thereafter counts of the numbers of viable organisms remaining were made by means of poured agar plates which were counted finally after 72 hours incubation Penicillinase was added whenever 0.01 u/ml or more of penicillin was present. Counts marked zero were usually checked by subculturing in broth and streak-

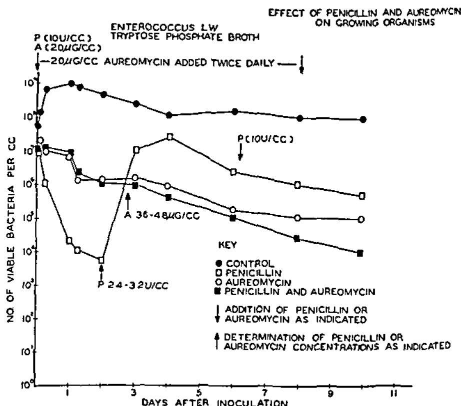


Figure 37

ing on blood agar plates Antibiotics were added to the flasks except in the experiments shown in Figures 37 and 38 at intervals as follows Penicillin 20 per cent of the original concentration per day, aureomycin 100 per cent twice a day, and terramycin 30 per cent per day, so as to restore the antibiotic levels approximately to their original values at intervals.

These quantitative studies of the effects of some antibiotics on enterococci are particularly interesting when correlated with clinical experi-

ence and with the results of the usual sensitivity tests, which measure only the bacteriostatic effect of drugs. If one were guided by inhibition tests the drug chosen would usually be aureomycin, terramycin, or chloramphenicol, for as little as 1 microgram per cubic centimeter of one or another of them inhibits the growth of most enterococci. Yet when we

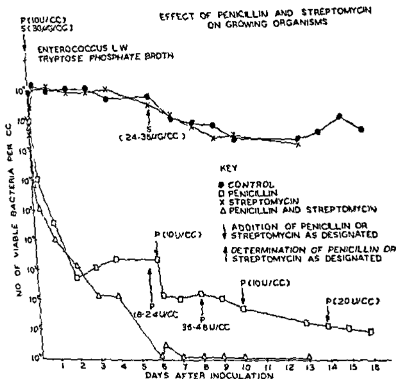


Figure 38

follow what happens to a bacterial population exposed to 10 or 20 times the inhibiting concentration of one of these agents (Figures 37, 39, 41) we see that many viable organisms persist for weeks If a similar effect exists in the vegetation it is then not surprising that a good many patients relapse after treatment with these static drugs.

Penicillin (Figures 37 and 38) in this case does somewhat better at first, but at a concentration of 10 units per cubic centimeter, which would correspond roughly with the average blood level attained by giving 10

Enterococcus (He.)

LOG VIABLE ORGANISMS /ml

DAYS AFTER INOCULATION

○ Control
▪ T'mycin (20 μg/ml)
● T'mycin (20μg)+S'mycin (20μg)
▫ T'mycin (20μg)+Pen (2u)

Figure 39

Enterococcus (He.)

LOG VIABLE ORGANISMS /ml.

DAYS AFTER INOCULATION

○ Control
▫ Pen (10u) + S'mycin (20μg/ml)
▪ Pen (20u) + S'mycin (30μg)
● Aureo (20μg) + S'mycin (30μg)

Figure 40

million units a day, one still does not kill all of the bacteria. This finding in turn fits with the clinical experience that massive doses of penicillin alone frequently fail to cure enterococcal endocarditis (3).

The effect of streptomycin is interesting and mysterious. By itself (Figure 38) no effect whatever on the growth curve of this organism is demonstrated, yet when streptomycin is added to penicillin (Figures 38

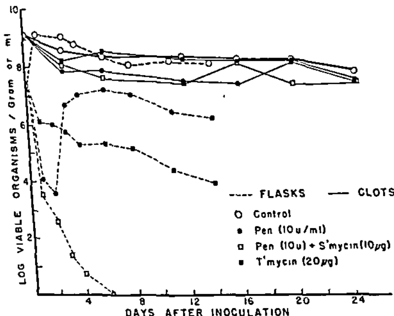


Figure 41

and 41) a rapid and complete killing of the whole bacterial population results Again the clinical results with this combination of drugs fit with the in vitro findings. Several reports from this country and from England (4, 5, 6) are in agreement as to the effectiveness of penicillin and streptomycin in the great majority of cases of enterococcal endocarditis

The effect of combining penicillin with one of the bacteriostatic agents —aureomycin, chloramphenicol, or terramycin—is difficult to evaluate at present because clinical data are largely lacking In vitro it has been shown (7, 8, 9, 10) that these agents all seem to interfere with the

early bactericidal effect of penicillin (Figures 37 and 39), but in some instances the bacterial population may eventually be markedly reduced. Success with this type of combination has been reported (11), but for the time being at least it seems advisable to use penicillin and streptomycin as the first choice.

From observation on the in vitro effects of adding streptomycin to aureomycin or terramycin (Figures 39 and 40) one would be encouraged



Figure 42

to try these combinations clinically Personally I have not done so, in part because Dr. Geracci at the Mayo Clinic informs me that he has had a number of clinical failures using terramycin and streptomycin. Cates (6) also reports success with penicillin and streptomycin after failure with aureomycin and streptomycin.

It is notoriously dangerous to attempt to predict the clinical effectiveness of an agent from in vitro observations alone, but so far as we have gone the correlation of in vitro bactericidal action with results in patients is fairly good. Discrepancies exist, however, and in an attempt to elucidate other mechanisms which might have bearing on the problem, we

have made some in vitro studies of the effects of antibiotics on infected blood clots.

The method is briefly as follows: 1 cc of an overnight culture of the organism is added to a series of 25 silicone-coated sterile Wassermann tubes to each of which is then added 2 cc of freshly drawn human blood. The tubes are then mixed and allowed to clot. When the clots have

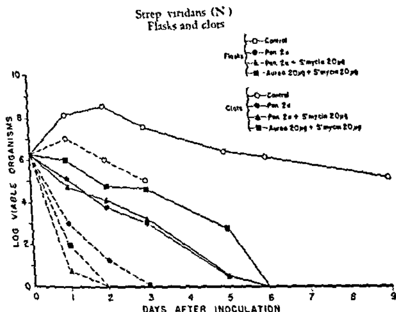


Figure 43

retracted they are removed aseptically and transferred to tubes of nutrient broth. Thus a series of infected clots approximating the size of a large vegetation and weighing about 1 gm is obtained. These are then incubated, and antibiotics are added to the surrounding media at intervals as in the previous experiments. The clots maintain their integrity for periods of weeks under these conditions, and individual clots from a series all exposed in the same fashion can be removed at intervals, weighed and ground aseptically. The numbers of viable organisms per gram can then be determined, and a growth or killing curve constructed which provides a measure of the ability of antibiotics to eliminate organ-

isms from a nidus of fibrin and blood cells. Figure 42 shows a low power photomicrograph of such a clot stained by the Gram-Weigert technique. The clot had been incubated for seven days, and aureomycin 20 micrograms per milliliter had been added twice daily to the surrounding medium. One can see masses of bacteria in the depths as well as a few in the surface layer of fibrin in spite of the fact that the organism is sensitive

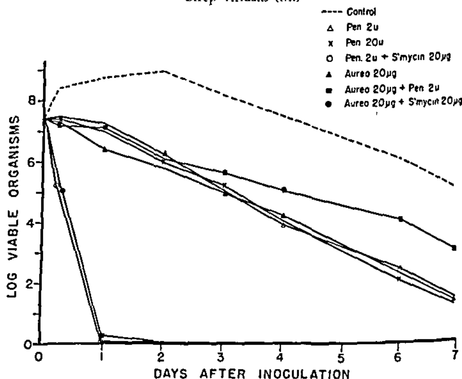


Figure 44

by inhibition test to about 1 5 micrograms per milliliter of the drug. The viable count on this particular clot was 7 million organisms per gram.

Figure 41 shows the marked protective effect of the clot which we have found for an enterococcus. One sees that although the organisms can be eliminated from liquid media in six days by penicillin and streptomycin, large numbers of viable organisms remain for as long as four weeks in the clots. The patient from whom this organism was recovered was cured by a six weeks' course of penicillin and streptomycin, however, which suggests that enterococci can be more readily eliminated

from patients' vegetations than from clots in vitro at least under the conditions of this experiment.

So far we have considered only the enterococci, and I think it is justifiable to stress infections caused by these organisms because of their refractoriness to the usual forms of therapy. Before leaving this subject it should be mentioned that occasional successes have been reported using truly heroic doses of penicillin alone [as high as 120 million units a day (12)] or in a few instances the combination of penicillin with bacitracin (13)

Next I should like to present some data on ordinary penicillin-sensitive streptococci of the viridans variety with the following problems specifically in mind. What accounts for the occasional failure of penicillin therapy in a patient harboring a "sensitive" organism? Does the addition of streptomycin to penicillin offer any promise in treating this type of infection? What type of action do the antibiotics singly and in various combinations have on Streptococcus viridans?

In Figure 43 we see the response of a typical penicillin-sensitive strain. It is killed in a few days by penicillin alone when grown in liquid media and survives only for about 1 week in clots. The addition of streptomycin does not speed up the death of the organisms appreciably. On the other hand Figure 44 demonstrates that penicillin is not rapidly lethal for all strains even at a concentration of 20 u/ml By inhibition tests this organism is as sensitive to penicillin as the first but it is killed much more slowly Furthermore the addition of streptomycin in this case greatly enhances the bactericidal activity of penicillin in a fashion similar to that observed for the enterococci Data on blood clots using these two organisms (Figures 43 and 45) demonstrate several points In the first place penicillin and penicillin with streptomycin are actively bactericidal in clots, but the latter afford some protection to the organisms and extend the time necessary for total killing of the bacteria two or more fold. Secondly, the strain variation noted in liquid media is still apparent but not so striking in the clot experiments Nevertheless in every case penicillin and streptomycin together are at least as effective as penicillin alone and often more rapidly and completely so (Figure 46). Thirdly, in Figure 45 it can be seen that a high concentration of penicillin is definitely more effective than a moderate one in sterilizing the clot, whereas in liquid media (Figure 44) the same organism is killed just as quickly by 2

units as by 20 units of penicillin. Incidentally these strains of Streptococcus viridans were recovered from a group of 5 patients, all of whom have been cured by a course of 2.5 million units of penicillin together with 2.0 gm of streptomycin daily for ten days. These organisms are all inhibited in vitro by 0.1 unit of penicillin or less.

The in vitro effects of aureomycin and terramycin on penicillin-sensitive strains are shown in Figures 47, 48, 49. In liquid media a bac-

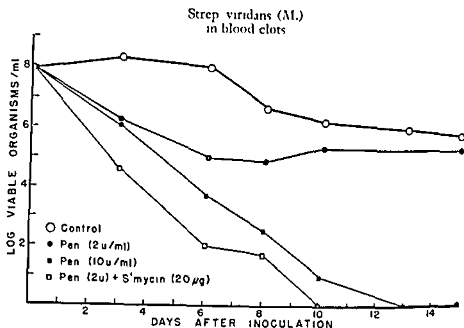


Figure 45

tericidal action is sometimes apparent (Figure 49), but bacteriostasis is the rule. The addition of streptomycin under these conditions usually results in rapid killing, again in spite of the fact that streptomycin by itself is usually ineffective. However, when the combinations of terramycin or aureomycin with streptomycin are tried on infected clots, the results are disappointing. Although aureomycin and streptomycin occasionally sterilize (Figure 43), the effects are usually those shown in Figure 50 where a marked protection of the organisms is apparent. Clinical data concerning the effectiveness of these combinations in patients are so scanty as to be of no great help at present, although a few failures with terramycin and streptomycin have already been alluded to.

Strep. viridans (F.)
in blood clots

LOG VIABLE ORGANISMS

O Control
• Pen (10 u/ml)
▪ S'mycin (20 μg/ml)
□ Pen (10u) + S'mycin (20 μg)

DAYS AFTER INOCULATION

Figure 46

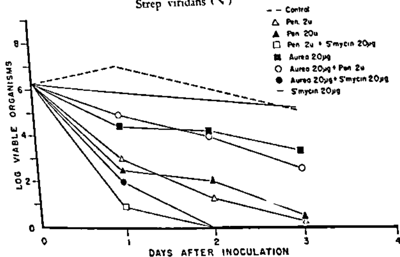


Figure 47

The mechanisms whereby organisms are protected in clots against various antibiotics in varying degrees have not yet been elucidated, but several possibilities come to mind. Variable diffusion into fibrin or chemical interactions with fibrin may play a role. A number of organisms are seen to be located intracellularly both in human vegetations and in infected clots, and it is possible that these intracellular bacteria may be

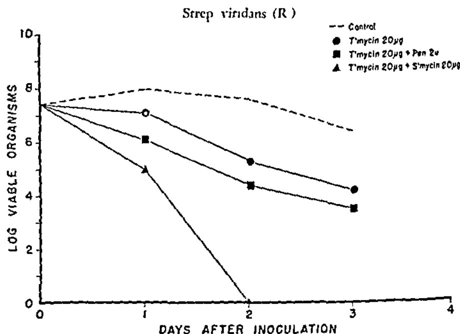


Figure 48

protected against some antibiotics and not others Lastly it is known that the metabolic and reproductive activity of bacteria influences very strikingly their susceptibility to antibacterial agents, rapidly multiplying organisms being, in general, more susceptible and resting organisms resistant. This is notoriously true of penicillin and in our hands is also true of other antibiotics. We have been unable to demonstrate total killing of resting populations of nonhemolytic streptococci by any antibiotic or combination of them which we have tried. It is not unreasonable to suppose that, in some areas of a vegetation or clot, organisms may be in a state of maximum population density and hence in a temporary refractory state.

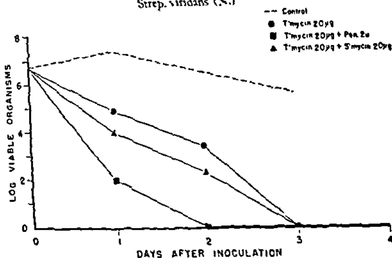


Figure 49

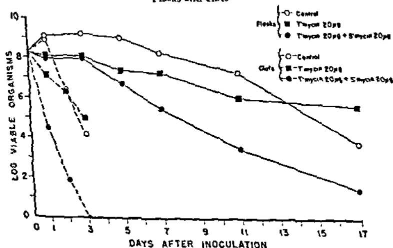


Figure 50

The practical implications of these observations and speculations are difficult to summarize. Perhaps the most important point to emphasize is that as new antibiotics come along, and many more undoubtedly will, their proper role in the treatment of bacterial endocarditis cannot be predicted by simply considering their inhibitory activity for nonhemolytic streptococci. The final court of appeal is of course clinical trial, but already the numbers of antibiotics and combinations thereof are so large as to force us to be selective in deciding what to try in patients. The studies reported herein are designed to give some leads as to possible means of selecting antibiotics which have a reasonable chance of proving effective in this infection.

Present evidence strongly favors the use of penicillin and streptomycin combined in enterococcal endocarditis. Optimal dosage and duration of treatment are not clearly defined, however, 10 million units of penicillin together with 2 gm of streptomycin daily for six weeks is probably the best current estimate. Although this regimen carries a high risk of damage to the vestibular apparatus, we feel that in such a serious infection taking this risk is justifiable.

In endocarditis caused by penicillin-sensitive organisms the evidence is not so clear-cut, but if it turns out that cure can be effected regularly in from ten days to two weeks using combined penicillin and streptomycin, the risk of encountering streptomycin toxicity will be small and the advantages over long courses of penicillin considerable.

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Chapter 15

HUMORAL AND VASOMOTOR CONTROLS OF BLOOD VESSELS*

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AT THE CORE of the problems of hypertension and shock lie the mechanisms which control the caliber of blood vessels. Whether blood pressure will be high or low depends on the content and caliber of arteries and arterioles and on their response to vasoconstrictor and vasodilator stimuli.

The three major groups of controls are the nervous system, the humoral system, and the system controlling the ability of the blood vessels to respond to stimulation. The first two stimulate pressor or depressor responses, but the latter regulates the degree to which response will occur. The total effect will depend, then, on the kind and intensity of the stimulus and on the responsiveness of the blood vessels.

The nervous control of blood vessels is a complex subject, grown so rapidly that it is too much to undertake in a limited discussion. I shall, instead, summarize contemporary knowledge of the humoral substances and forces which control reactivity

Humoral Control

All that is currently known is that a variety of pressor, depressor, vasoconstrictor, and vasodilator substances exist in many organs. The part they play is little understood. They must be in some sort of equilibrium, just as are substances maintaining respiration.

Few of them have been characterized chemically and methods for their quantitative determination are inadequate. For the most part, it has been common custom to give a physiological phenomenon or a

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pharmacologically active extract a name and relax on the hypnotic effect thereof for some years. I refer, for example, to "urohypertensin," "vagotonin," and the like. But there are notable exceptions. Who would have believed five years ago that the noradrenaline of the pharmacologist and the benzodioxanes of the chemist would be part of the common and necessary knowledge of the average internist?

Insofar as possible, the pressor and vasoconstrictor substances are divided according to their probable origin.

1. *Renal origin* Renin, a proteolytic enzyme, contained in tubular cells, acts on a protein, renin-substrate, to yield angiotonin or hypertensin. The substrate is a globulin which originates in the liver. The best evidence indicates that angiotonin is a peptide, though this is not established with certainty. So far, only biological assay of its pressor action is available for its semiquantitative determination. Despite valiant efforts by Taquini, quantitative methods for renin, based on angiotonin formation, are still inadequate They do not give any clear idea of how it functions in the normal control of the caliber of the vascular system. Its isolation has very nearly been accomplished by Haas and Goldblatt in California

Renin when injected into desoxycorticosterone acetate-treated rats causes a syndrome like eclampsia {Masson, Corcoran and Page (1)} It has many other interesting physiological properties, such as eliciting diuresis, proteinuria, and natriuresis (2) Its several properties seem to qualify it as a presumptive central participant in vascular disease This view is shared by our able colleagues in South America, Drs. Braun-Menendez and Fasciolo

In my opinion there is more evidence in favor of the possibility that renin, and therefore angiotonin, is an integral part of the mechanism of renal hypertension than any other currently suggested substance. It should not be overlooked that Grollman and Drury especially, are of contrary opinion

The "sustained pressor principle" of my colleagues, Helmer, Shipley and Kohlstaedt (3), has properties that suggest it has close relation but not identity with renin. It acts almost exclusively in nephrectomized animals in which it gives a greatly prolonged rise in blood pressure. Whether it acts enzymatically to produce an effector substance is not known

Vasoexcitor material (V.E.M.) of Shorr and Zweifach (4) is demonstrated in plasma by determination of the reactivity of metarterioles to topically applied adrenaline and the effect thereon of the injected test plasma. V.E.M. increases sensitivity to the adrenaline. Whether V.E.M. affects the general circulation, and in what manner, remains to be determined. In certain phases of hypertension, plasma V.E.M. concentration seems to be greatly elevated.

A variety of pressor amines, e.g., hydroxytyramine, have been thought to be liberated from the kidneys in greater than normal amounts as a result of inadequate deamination. This thesis remains unproved and is currently receiving little attention.

The problem thus remains entirely fluid, and current evidence does not justify ruling these substances in or out, either in the maintenance of normal blood pressure or in hypertension.

Pherentasin, presumed to be of renal origin, is a substance separated from plasma by Schroeder and Olsen (5). They believe it to be an amine. It seems to be present in increased amounts in a few normotensives, and in practically all hypertensives' blood with the exception of those of "neurogenic" and "endocrine" origin and those with malignant hypertension. Schroeder finds large quantities only when some renal impairment is present A good correlation between the presence of V.E.M., as demonstrated on the rat's mesoappendix, and the presence of hypertension and the occurrence of pherentasin was found If it is true, as stated unequivocally by Schroeder (6), that the blood of patients with severe hypertension contains large quantities of pherentasin and a V.E.M.-like material as well, the problem of renal humoral agents is on the way to solution

2. *Adrenal origin.* The story of adrenaline and noradrenaline in relationship to nerve transmission and the pheochromocytoma has been told so often it needs no repetition here The names of von Euler and Holtz, and later Goldenberg, Burn, Tullar, and Holton have become associated indissolubly with this story Some confusion exists in the use of the so-called "blocking agents" such as benzodioxane and tetraethylammonium as diagnostic tools, chiefly, I think, because enough attention has not been paid to their pharmacology. Under several circumstances, these agents may become pressor rather than exhibit their more usual depressor action.

Desoxycorticosterone-like corticoids are believed, chiefly as the result of the fine experimental work by Selye (7), to be intimately concerned in the production of vascular disease and hypertension. The evidence is largely from the effects of D.C.A. itself on uninephrectomized rats fed saline. Whether this applies to man remains to be investigated, and we shall await the results of work such as is being conducted by Dr. George Perera in New York and by Dr A. C. Corcoran in our clinic, with great interest.

It seems unlikely that steroids are directly pressor, rather their action on the blood vessels is indirect. It remains to be proved whether the overproduction of D C A.-like steroids is primarily responsible for human essential hypertension, or if not primary, to what secondary degree they are involved The hypertension of Cushing's syndrome with its adrenal cortical hyperfunction may have such a mechanism

3. *Cerebral origin* Study of the effect of humoral agents on the vasomotor control of the brain and the liberation of vasoactive substance from brain and nerve has been but little prosecuted. Pressor substances have been detected in cisternal fluid and brain substance of human beings and animals, but their chemical nature has not been elucidated. Pitressin seems to appear irregularly in cerebrospinal fluid

It is of interest that stimulation of the central end of the cut vagus or sciatic nerve causes the liberation of a substance which can be transferred from the brain of the stimulated animal into a recipient, eliciting a large and prolonged rise in arterial pressure. The pituitary gland does not seem to be its source. Agents which reverse the pressor action of noradrenaline and adrenaline do not do so with this substance. Hydrazino phthalazine has been found to block its action (8).

About fifteen years ago I separated a highly active pressor substance from cisternal and occasionally from spinal fluids (9) Absence of the pituitary gland did not prevent its appearance It was alcohol- and water-soluble and not protein in character. Some of its pharmacological properties were those of adrenaline but others differed. Noradrenaline was not available at the time so no comparison was made. Raab (10) has recently also obtained good evidence that a sympathomimetic substance occurs in all parts of the human and animal brain It has some chromogenic and pharmacologic properties in common with both adrenaline and noradrenaline.

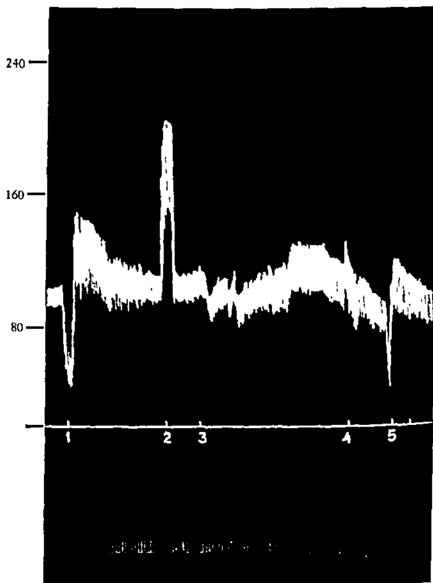


Figure 51. Effect of 5-hydroxytryptamine injected intravenously into a dog with spinal cord cut at C_6. No anesthesia. (1) 5-hydroxytryptamine 100 μg, (2) noradrenaline; (3) infusion of Priscoline 5 mg/kg plus Benodaine 3 mg/kg started, (4) noradrenaline, (5) 5-hydroxytryptamine.

Obviously it is impossible currently to evaluate any etiologic significance these substances might have. This does not detract from the intriguing investigative approaches offered by the occurrence of these materials.

4. *Uncertain* For many years physiologists had known that when blood clots it also becomes vasoconstrictor. They also knew that to perfuse organs successfully it was necessary to insert a pair of lungs in the circuit This problem was not of great import to us until we developed a rather elaborate modification of the simple Pissemsky ear perfusion with the object of determining the vasoconstrictor properties of hypertensive blood (11). We could never be sure how much vasoconstriction might be due to undetectable coagulation, so the vasoconstrictor itself was studied.

Rapport, Green, and Page (12, 13) reported in a series of papers the isolation, crystallization, partial structure, and some pharmacological properties of the vasoconstrictor substance. The name *serotonin* was given the indole amine. Rapport (14) suggested that the substance might be a complex compound of equimolecular parts of creatinine, sulfuric acid, and 5-hydroxytryptamine. This seems to have been confirmed by its synthesis by Hamlin and Fischer (15). Dr. Hamlin kindly sent me 60 mg of the synthetic material It proved to be slightly more active than adrenaline as a vasoconstrictor in the perfused rabbit's ear vessels and about ten times less active than adrenaline as a pressor agent when injected intravenously into cats and dogs This, among other properties, suggested that pharmacologically it was very similar to, if not identical with, the naturally occurring serotonin as shown in Figure 51.

There is little known about the function of this substance. Since it is liberated when blood clots, presumably it is concerned with the prevention of bleeding by causing the blood vessels to constrict down on the forming clot. It has some similarity to the pressor substance liberated from the brain on afferent stimulation.

The presence of adrenaline and noradrenaline-like substances in heart muscle [see Raab and Lepeschkin (16) for excellent review] and possibly in blood vessels must have some significance, but currently it is unknown Von Euler (17) concluded that the sympathomimetic actions of heart muscle extracts, as well as many other tissues, are due chiefly to noradrenaline. Raab and Lepeschkin (18) suggest that both adrenaline and noradrenaline elicit hypoxia of the heart muscle by chemically inducing an excessive and wasteful oxygen consumption in the myocardium, irrespective of coronary blood flow

Depressor Substances

Depressor substances have for the most part been so poorly defined that the names so lightheartedly conferred on them are almost wholly unjustified. Almost nothing of their origin is known.

Histamine occurs in nerve tissue, in white blood cells, plasma, and possibly red cells. So far no evidence has appeared that an abnormality of its metabolism exists in hypertension. Whether it aids in the maintenance of normal blood pressure is not known Adenylic acid and adenosine are both active depressor substances, but their association with humoral control of hypertension has not been adequately studied. Acetylcholine is familiar as the mediator of parasympathetic nerve impulses, and, like the previous substances, has not been shown as yet to be concerned in the mechanism of hypertension. Probably its concern with nerve transmission, especially in autonomic ganglia, gives it a key position in control of vascular reactivity, as we shall see later.

Vasodepressor material (V.D M.) has been identified as ferritin by Mazur and Shorr (19). V.D M is believed to depress the reactivity of blood vessels of the rat's mesoappendix to adrenaline, to be significantly reduced in some stages of hypertension, and to be greatly elevated in shock. Ferritin has not been demonstrated to affect blood pressure itself, nor does it depress the reaction of the arterial pressure to injected adrenaline or noradrenaline.

Carbon dioxide in some concentrations is a pressor substance while in others is a depressor. Unless the conditions are carefully defined, it is not possible to predict whether blood pressure will rise or fall on its administration Being constantly present, it would be expected to be a controlling force in the regulation of blood pressure.

Clearly, investigation of depressor substances has but begun It is hard to believe they are less important than pressor substances.

Vascular Reactivity

Substances believed to affect blood pressure by either cardiac and/or blood vessel stimulation have been cursorily reviewed. The assumption is always implied that these organs respond in a uniform fashion. The smallest experience in the physiology laboratory shows this to be untrue. Table VII demonstrates average values for the responses of normal dogs

under pentobarbital anesthesia to standard doses of vasoactive drugs. The great spread is evident. We have studied the mechanisms of these variations in reactivity for a number of years, and it is to this problem that we will now briefly turn.

Examples of the extremes of vascular reactivity occur in shock, where it is exceptionally low along with hypotension; after denervation of blood vessels where it usually is exceptionally high, along with labile hypertension, as in paraplegia. It should, however, be emphasized from

TABLE VII

Examples of the Range of Normal Reactivity (in mm Hg) in Dogs

	Low	*Medium*	*High*
Adrenaline	4	30	72
Noradrenaline	20	73	118
Barium chloride	0	21	64
TEAC	−20	−43	−60
Veratrum	0	−31	−68
Azide	−26	−42	−64
Angiotonin	4	22	48

the outset that there is no direct and obligate relationship between the height of arterial pressure and vascular reactivity. Reflection on the multiplicity of factors which control the height of blood pressure indicates why this must be true

Control of Vascular Reactivity

1. *Neurogenic*. It is generally recognized that sympathetic denervation results in increased reactivity of blood vessels, a phenomenon extensively studied, especially by Cannon and Rosenblueth There is no need to review this problem as it has already been done in masterly fashion by Rosenblueth (20) Thus total dorsolumbar ganglionectomy results in a very significant increase in blood pressure responses when such substances as adrenaline, noradrenaline, barium chloride, and angiotonin are injected intravenously In the following studies, I shall refer to this type of over-all vascular response of the animal as a measure of vascular reactivity. Fortunately, for simplicity, the heart and blood vessels often parallel one another in their reactivity changes

There are other ways of accomplishing much the same thing as surgical "total" ganglionectomy Injection of tetraethylammonium chloride

and hexamethonium are now widely familiar methods of eliciting ganglionic blockade. As we were able to show (21) after such blockade, reactivity rises immediately and greatly, just as it does several days after ganglionectomy. This suggests that changes in the humoral environment of the autonomic ganglia can exert a profound effect on the reactivity of the cardiovascular system, a concept almost wholly ignored in its relationship to vascular regulation.

If blockade causes increased reactivity, then would stimulation of autonomic ganglia decrease reactivity, and is stimulation ever elicited by the usual constituents of the body?

We studied (22) this problem in curarized dogs breathing CO_2. A moderate or sharp fall in arterial pressure occurred, and almost immediately responsiveness to stimulation by chemical agents disappeared or was sharply reduced. It was as though the ganglia had suddenly rained down a shower of inhibitory impulses which blocked peripheral vascular responsiveness. Administration of tetraethylammonium during this period rapidly, but not wholly, restored responsiveness. But lumbodorsal ganglionectomy abolished altogether the ability of CO_2 to cause refractoriness. It is for such reasons that the ganglia seem so important a part of the neurogenic component controlling vascular reactivity.

Another approach to the problem consists in section of the buffer nerves, i.e., the carotid sinus and aortic depressor nerves, thus producing neurogenic hypertension. A curious change in vascular responsiveness occurs as a result In normal and renal hypertensive animals repeated intravenous administration of tetraethylammonium chloride (TEAC) results in progressively lesser falls in arterial pressure until pressor responses occur. In contrast, dogs with buffer nerves sectioned show little or no tendency to reverse from depressor to pressor. Each dose of TEAC is followed by a sharp fall in blood pressure, each one like the other. The same reaction pattern has been detected in some hypertensive patients as McCubbin and I found (23).

In essence, we have interpreted this phenomenon as a change in the ability of TEAC to block sympathetic ganglia as a result of loss of the buffer nerves. It furnishes another example of the profound effect extraganglionic control may have on the ganglia themselves and thus indirectly on the reaction of the blood vessels.

We conclude that both the buffer nerves and CO_2, among other in-

fluences, may alter autonomic ganglia as indicated by changes in the response of the blood vessels.

The brain also seems to contain chemoreceptors which may influence the response of blood vessels (Taylor and Page) (24). Dogs were prepared by isolating the cerebral circulation completely from the body but leaving the nervous system intact, except for denervation of the carotid sinuses and bilateral vagus section. The brain was perfused by a donor dog Substances injected either into the donor dog or directly into the arterial circulation of the brain could act only through the central nervous system of the recipient animal.

Injection of depressor substances such as histamine or acetylcholine elicited rises in blood pressure contrasting with adrenaline and noradrenaline, which produced falls. Thus, substances usually considered pressor became depressor and vice versa when they acted directly on the brain. We have, therefore, concluded that the brain contains a system of chemoreceptors not heretofore described The part they play in the over-all regulation of the response of the circulation to stimulation remains to be determined.

The carotid sinus and depressor nerves have an important influence on reactivity, but purposely I omit discussion of them until their actions are much better known and because they are now under active investigation in several laboratories.

There remains one more well-defined component of the nervous control of the blood vessels. It consists of that outlying, intricate, chemical regulatory station, the myoneural junction, and its control of responses of vascular muscle These receptors seem to be endowed with extraordinary *properties*, but I shall consider only one as an example of how they may be influenced to affect vascular response.

Infusion of Benzodioxane, Dibenamine, or Regitine results in rapid inversion *of the* pressor adrenaline response to depressor and the slow inversion of that to noradrenaline. This occurs whether the vessels have central nervous connections or not But the response to substances such as angiotonin, sodium nitroprusside, and barium chloride are unchanged. Clearly, it is possible to influence the vascular response in a highly specific fashion by substances which act at the myoneural junction These junctions thus *offer* another point where vascular reactivity may be affected by what circulates in the blood.

2. *Humoral.* There are organs other than the nervous system that, having no direct connections with the blood vessels comparable to nerves, nevertheless influence their reactivity by humoral action. This whole complex regulatory system has not been recognized until very recently and has been little studied.

Nine years ago we investigated the responsiveness of blood vessels by injecting a variety of chemicals during the course of hemorrhagic and traumatic shock and later extended it to hypertensive animals (25, 26). There was no doubt that as shock deepened, at first partial, then complete, vascular refractoriness appeared. Failure of blood vessels to respond has seemed a cogent reason for the failure of recovery in terminal shock. Indeed, to us it has remained one of the key problems of shock which has received no solution and relatively little investigation.

(a) *Liver.* Loss of this organ profoundly affects vascular reactivity in a fashion not unlike that which develops as shock deepens. For several hours after removal, it is normal, then despite treatment with whole blood, glucose, and salt, reactivity gradually is lost and arterial pressure falls concomitantly (27). We have so far found no way to restore reactivity or to prolong life. Whether the liver produces some substance vital to the mechanism for vascular contraction or must remove some noxious agent remains to be determined

(b) *Kidneys* It has been known for some time that bilateral nephrectomy intensifies the pressor action of renin and angiotonin. Other substances also may be augmented. There seems to be no direct relationship between the heightened reactivity and the concentration of retention products As with the liver, it is not clear whether the destructive or excretory chemical functions of the kidneys are involved. Currently all we can say is that when dogs are kept alive by peritoneal lavage or the Kolff artificial kidney, the heightened responsiveness does not appear [Page and Kolff (28)]

(c) *Adrenals.* The extended studies on the effect of the adrenal glands by many investigators must be passed over with the statement that loss of the whole gland without replacement therapy gradually causes loss of reactivity. It is not of the degree seen after hepatectomy Complete restoration is achieved by treatment with cortical steroids.

Although there is evidence to the contrary, we have not been able to demonstrate any clear effect of injected DCA on reactivity of normal

or uninephrectomized-salt-treated dogs [Masson, Page, and Corcoran (29)]

(d) *Thyroid*. Complete suppression of thyroidal function in normal dogs sharply reduces vascular reactivity [Page and McCubbin (30)] which is only partly restored by feeding large doses of thyroid powder. In both neurogenic and renal hypertensive dogs, athyroidism is associated with only minor changes in reactivity and no significant decrease in blood pressure. Even slowing of pulse rate in neurogenic hypertensive dogs, which occurred several months after suppression of thyroidal function, did not reduce arterial pressure.

(e) *Pituitary*. We studied vascular reactivity in dogs a number of years before and after hypophysectomy. The results showed no impressive changes. Even when there had been accompanying diencephalic injury followed by marked obesity, vascular reactivity fell off only moderately.

Arterial Hypertension

The response of the arterial pressure to a variety of drugs acting on different parts of the vascular tree may be employed to determine the contrasting mechanisms of chronic hypertension experimentally produced in dogs The results in the types of hypertension studied suggest that the pattern of response depends on the state of the extrinsic regulatory mechanisms of the blood vessels rather than on intrinsic change in vascular musculature [Page and McCubbin (31)].

Contrasting with chronic experimental renal hypertension, greatly increased vasomotor function in chronic neurogenic hypertension causes increased peripheral resistance Thus the response pattern to such drugs as TEAC, the hydrogenated ergot alkaloids, and hydrazino phthalazine is very different in primarily neurogenic hypertension from other non-neurogenic varieties. Some patients also show this differentiation, suggesting primacy of neurogenic mechanisms. Obviously, the purpose of this method of study is to find response patterns in patients which correspond with those in animals in which the mechanism is known or ascertainable.

TEAC has been employed in interesting studies by Ferris and his associates Brust and Assali (32) to evaluate in patients the degree of neurogenic and humoral participation in blood pressure maintenance in

normal and toxemic pregnancy. The results, so far, suggest predominance of humoral control in toxemia.

The body faces an extraordinarily complex problem in the distribution of blood according to need. It should not, therefore, be surprising that complex systems of control are employed. To unravel this complex and resynthesize it, the system must be artificially pulled apart and studied as though the components were independent of one another, a condition inconceivable in the whole animal.

Conclusions

Substances which seem likely to be concerned in the control of caliber of blood vessels are of renal, adrenal, and nervous origin, while a few are of uncertain origin. The pressor agents are better characterized than the depressor, but surely the one group is no less important than the other.

Integrated with the system of substances which cause pressor and depressor effects are those which control reactivity of the blood vessels; a highly complex system with widespread roots in the body. The nervous system—especially the autonomic ganglia, carotid sinuses, and cerebral chemoreceptors—the liver, and kidneys play important parts in this regulation. It is the interplay of stimulating and depressing forces acting on blood vessels of changing responsiveness which determines blood flow and pressure.

The relation of these investigations to clinical hypertension is somewhat obscure but that ultimately one will be demonstrated can hardly be doubted. Enrichment of knowledge of the basic mechanisms controlling blood pressure and blood distribution must at least equal those leading to empirical treatment of hypertension.

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Chapter 16

ENDOCRINE FACTORS IN HYPERTENSION *

George A. Perera †

DURING THE LAST few years, among other new developments in the hypertensive field, three topics have received an unusual amount of study and publicity, all related in some way to substances elaborated by endocrine structures. And so I plan to talk about the psyche, stress, and steroids in relation to hypertensive vascular disease.

It is an accepted fact that emotional reactions may exert profound effects on the arterial pressure, particularly on the systolic level These effects are brought about by increased cardiac action and vasomotor modification, largely as a result of the liberation of epinephrine. Not only can environmental factors, fear, excitement, and repressed as well as expressed emotions raise the blood pressure—in hypertensives even more than normotensives—but it can be said with equal authority that their relief or removal may reduce levels to an extent as dramatic as that produced by many of the more powerful drugs at our command Without hesitation, one can state that psychological influences are of major importance, and that application of this knowledge provides a means whereby many of the clinical manifestations of hypertensive vascular disease can be reversed readily Our problem is to decide whether special etiological or therapeutic significance should be attached to these established facts

There are two extreme attitudes taken by some individuals in the field. The first, championed primarily by psychiatrists, would have us believe that the entire sequence of events in essential hypertension is initiated

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by some antecedent emotional disturbance or characteristic personality pattern. The second, presented chiefly by internists, would attribute the whole process to an organic vascular disease, related perhaps to hereditary factors, but with no contribution from the psychological sphere. Some adherents of the former view have described a unique pattern, characterized by exaggerated dependent strivings, submissiveness coupled with stubbornness, suppression of hostility, and so forth. But here we step into a highly controversial field. The occasional reality of such patterns and the somewhat higher incidence of various forms of neurosis in association with hypertension cannot be denied. However, the number of patients studied is scarcely sufficient to lend statistical validity to such a correlation, and similar patterns have been portrayed in other conditions. Furthermore, it is difficult to avoid retrospective conclusions, to remain objective, and to obtain satisfactory control studies when dealing with the complexities of human nature in a complex disease state.

The position, that hypertensive disease has a psychosomatic component, now has some experimental support. Favoring the existence of neural and autonomic mechanisms, activated by emotional factors, is the observation that norepinephrine from the adrenal medulla is a pressor substance. Since some patients show a persistent residual hypertension even after the removal of a pheochromocytoma, Goldenberg and his associates (1) raise the question that frequent or prolonged secretion of adrenergic agents may set into action a self-perpetuating process. A new observation has been provided by Page and his colleagues (2) who recently reported that the brain, on appropriate stimulation, can elaborate a pressor material.

On the other hand, the hereditary nature of essential hypertension cannot be ignored and has been utilized as an argument against a strictly emotional basis for the disease. In addition, we have seen striking changes in emotional reactivity appearing coincidently with the onset of hypertensive disease even without the patient's knowledge of an elevated blood pressure. This "emotional decompensation" may be restored at times by sympathectomy. Intensive psychotherapy will lower the blood pressure in essential hypertension (as will rest, sedation, and many other drugs and procedures), nevertheless, detailed study before and after such treatment has indicated lowering of pressure ceilings rather than of floors—but no established effect, to my knowledge, on the underlying

disease or its rate of progression. Admittedly, these observations do not exclude the possibility of antecedent psychic trauma, or the added possibility that repeated emotional crises in a sensitized subject result finally in an irreversible organic sequence They do suggest, however, that no rigid position is tenable at the present time. Hypertensive vascular disease involves multiple considerations, and perhaps multiple components produce its final clinical and pathological picture We have no right to dismiss any approach which might prove fruitful. This problem cannot be settled until it is approached with scientific methods, with the same appreciation of physiological variables, with the same critical evaluation and control studies as those employed in any other field of research effort. Only when these have been applied will we have the right to take a definite stand.

In modern medical parlance, the word "stress" has replaced "stimulus" and in the minds of some has become synonymous with the adrenal cortex. Selye (3) has defined it as "a condition, due to function or damage, which causes extensive regions of the body to deviate from their normal resting state" It could be suggested, however, that stress constitutes any change in the external or internal environment of sufficient magnitude to invoke a bodily alteration, i.e., flashing a light in the eye with resultant pupillary constriction To Selye, after the major contributions of Claude Bernard and Walter Cannon, belongs the commendable credit for the more elaborate picture of the response to stress—the alarm reaction—but he would have us believe that nonspecific stress, through adrenal cortical participation, may produce hypertensive vascular disease and many other disorders from tonsillitis to adiposity

Is stress important in the etiology of essential hypertension? Several investigators have confirmed the observation that pathological changes including an elevated blood pressure can be produced by appropriate stimuli. It must be kept in mind, however, that chronic elevations of blood pressure have been achieved only in the presence of added renal damage or in the course of the administration of excessive and unphysiological doses of endocrine preparations. Not only do pathological changes after stress require highly abnormal conditions, but they have been encountered in the exceptional animal, not as a rule, and control animals sometimes exhibit these same pathological changes

The weight of evidence points toward the pituitary-adrenal axis only

as an important adjunct to the response of tissues. An excess of adrenal cortical materials is not essential for the response to stress, inasmuch as patients with Addison's disease can develop hypertension, rheumatoid arthritis, nephrosclerosis, and many other so-called diseases of adaptation, and even adrenalectomized animals can be made hypertensive (4). We have studied a patient with both hypertensive vascular disease and Addison's disease, who also had diabetes mellitus and rheumatoid arthritis (5). On two separate occasions a high sodium chloride intake failed to modify the blood pressure. On the other hand, when maintained on constant small amounts of desoxycorticosterone daily, the blood pressure rose with an increased intake of salt and fell when the salt dosage was reduced. Certainly an excess of adrenal cortical hormones was not responsible for the restoration of the hypertension in this situation. As yet there is no evidence which establishes maladaptation to stress as a cause of disease It remains merely an interesting and attractive bit of theoretical speculation

Now let us turn to the endocrine structures themselves. Is there any evidence that their secretions, and particularly those of steroid composition, play a primary role in the etiology of essential hypertension? We need not consider the thyroid, parathyroids, or gonads. Cushing's syndrome has been observed in several patients with carcinoma of the thymus, but this must be regarded as coincidence until proven otherwise. The literature abounds with references of hypertension in association with diabetes, but when clinical data are reviewed, documentation obtained, and post-mortem material studied, one can establish that the incidence of true hypertensive disease is only slightly greater. The blood pressure changes among diabetics are due in large part to secondary arteriosclerotic complications Although the posterior pituitary elaborates a pressor material, antidiuresis appears long before dosage is sufficient to modify blood pressure, the absence of fluid retention in hypertensive subjects leaves little need for consideration of this area. And finally, although hypophysectomy may have some effect on experimental hypertension, we have been unable to confirm the alleged relationship between acromegaly and hypertension and have found many instances of coexistent hypopituitarism and hypertensive disease.

Mention has been made already of the adrenal medulla and its norepinephrine, which can elevate the arterial tension through modification

of peripheral resistance when administered in appropriate doses. An excess of circulating norepinephrine can be excluded as a cause for hypertensive vascular disease, both by direct analysis and the fact that the benzodioxane drugs fail to lower blood pressure in patients with this disorder. Nevertheless, the possibility must still be entertained that sensitization of blood vessels to normal amounts of norepinephrine could account for hypertension (1, 5, 6), and that we are not entitled as yet to eliminate the adrenal medulla from further consideration.

The adrenal cortex entered the hypertensive story in 1897 with the first description of pathological changes associated with certain adrenal tumors. Many additional evidences of a relationship have been provided since that time (7). The hypertension of Cushing's syndrome, the hypotension of Addison's disease, and the frequent elevation of blood pressure in Addisonian patients treated with maintenance doses of desoxycorticosterone are all well-documented and accepted observations. In addition, the adrenal cortex has been involved in experimental studies concerning the kidney-derived vasotropic principles, experimental renal hypertension, pressor amines, norepinephrine sensitivity, and many others. Furthermore, adrenal cortical changes have been described in animals on a reduced or excessive salt intake—of interest in connection with the effects of diet on blood pressure.

During the past eight years, together with Dr. Kermit Pines and others, we have pursued this problem through the technique of balance studies undertaken in a metabolic unit on patients with documented and usually uncomplicated hypertensive vascular disease. Some of our results have been independently confirmed and extended along new lines by means of animal studies conducted by Drs. Knowlton, Seegal, Loeb, and Stoerk. The combined results on steroidal modification of blood pressure are shown in Figure 52. It must be emphasized that this summary chart reflects certain dosages of steroid, under constant, quiet, and controlled hospital conditions, and over certain specific periods of time. It might require modification if other conditions were employed. Presented in this form, however, it serves the purposes of this discussion.

It should be noted first that the addition or subtraction of dietary salt has a small but consistent effect on the blood pressure of uncomplicated hypertensives but is without effect in normotensives. Nor does an excessive salt intake influence the arterial tension in a hypertensive with

adrenal cortical insufficiency unless small, daily injections of desoxycorticosterone are administered. These observations suggest that the sodium ion is related to blood pressure regulation, that the hypertensive handles salt or its restriction in a manner different from normal, and that an intact adrenal or some exogenous steroid is necessary for this action.

	NORMAL	HVD	ADDISONS	ADX. RAT	HVD + ADDISONS	RENAL DAMAGE	ADX. RAT + EXP NEPHRITIS
NaCl	0	↗	0	0	0		↗
DCA	↗	↗ †	↗	↗	↗	↗	↗
CORTISONE *	0	↘	↗	↗	↗	↗	↗
CPD F *	0	0			↗		
ACE	0	↘				0	
—NaCl	0	↘					
DCA—NaCl	0	0		0			
CORTISONE—NaCl	0			↗			
DCA + CORTISONE			↗		↗		
DCA + CPD F	↗						
DCA + ACE		0					

* 100 mg or less
† May be transitory

Figure 52

Desoxycorticosterone—but only in the presence of at least some dietary salt—raises the blood pressure under all of the circumstances tested, 40 mg being no more effective than 4. However, the pressor response is faster and greater in adrenalectomized animals, in Addisonian man, or in the face of renal damage than it is in normals, and dissimilar to the response in hypertensives Patients with hypertensive disease under these relatively basal conditions of study, invariably get an immediate small rise in arterial tension, but this is usually transitory over a period of a week or so. We recently had occasion to find this hypertensive pattern in a woman with a repeatedly normal blood pressure who only at a later date developed a persistent increase in pressure; in

other words, an abnormal response to desoxycorticosterone may precede the onset of overt disease (8). From this group of studies, the pressor properties of at least one steroid are confirmed, but again we find that the normal differs from the hypertensive.

Unlike desoxycorticosterone, at least in the adrenalectomized rat, little or no salt is required for the pressor effect of cortisone (9). But similar to desoxycorticosterone, adrenalectomized animals, Addisonian patients, and subjects with renal damage of many varieties (with or without hypertension) show the most pronounced responses. Normals exhibit little or no change with comparable dosage and duration of treatment, and uncomplicated hypertensives may even show a slight fall in blood pressure The close structural similarity of Compound F (17-hydroxycorticosterone) to cortisone, its almost equal ability to produce hyperadrenalism and modification of rheumatic disorders, as well as our preliminary investigations of its action (10), would lead us to suspect that its properties are similar Thus we have other steroids which can be pressor under certain conditions, and once more an agent producing different effects under the influence of different disease states

Is it conceivable that the adrenal cortex secretes some other substance capable of counteracting the effects of pressor hormones? This is suggested by the augmented action of cortisone in the adrenalectomized animal and in Addison's disease, by the studies employing adrenal cortical extracts in hypertensives, and by the apparent blocking effects of such extracts when given simultaneously with desoxycorticosterone (7). It is, however, far from established Extracts contain many unknown ingredients Furthermore, the interpretation of steroid action must be made with extreme caution. An administered agent may modify anterior pituitary secretions and alter the character of the existing adrenal hormones Moreover, little is known concerning the pathways of degradation and the possible physiological actions of such by-products of metabolism.

Beyond doubt, the adrenal cortex plays a part in the regulation of blood pressure. Beyond doubt, the mechanisms involved are complex and not due to direct humoral action inasmuch as changes in arterial tension require days, not minutes, and are scarcely proportional to dosage Could hypertensive vascular disease be the result of an overproduction of some adrenal cortical hormone? Although the cortisone-like Compound F is

now regarded as of definite adrenal origin, an excess gives rise to all the manifestations of hyperadrenocorticalism or Cushing's syndrome. These are not generally observed in essential hypertension. Only by postulating its conversion to another pressor agent, or by adding the concept of a simultaneous change in some other adrenal product, could such a theory be entertained at all. What about an excess of some desoxycorticosterone-like hormone, for desoxycorticosterone appears to be required for the maintenance of hypertension in the hypertensive Addisonian? Then 1 or 2 mg must represent an excess, for massive doses exert no greater effect. This could account for hypertension, and the diminished influence of this steroid in hypertensives might be interpreted as indicative of a state in which an excess is already present, but such a theory fails to explain the pressor action of cortisone. Nor can it be said with certainty that the adrenal cortex makes desoxycorticosterone. There is no definitive answer as yet, no proof of adrenocortical dysfunction in hypertensive disease has been provided by existing tests, and we must await the development of methods by which desoxycorticosterone-like compounds in the adrenal and circulation can be quantitated accurately.

Whether or not there is a possibility of hypertension of adrenal origin, it is clear that some types of hypertension can appear or be maintained in animals and in man in the absence of intact adrenals Abnormal elevations of blood pressure have developed in Addisonian patients following renal damage by disease (7), and bilaterally adrenalectomized rats become definitely hypertensive in response to cytotoxic serum nephritis providing a satisfactory nutritional state is maintained and a high sodium chloride intake employed (4)

Despite the enthusiasm of recent years, it must be admitted that hormones function chiefly in an expediting capacity, as regulatory superstructures. They modify rather than initiate basic metabolic processes. Several recent developments of possibly great significance indicate that renal hypertension may represent the retention of a pressor substance which is normally excreted (11, 12). Handler and Bernheim (12) have presented evidence that at least one form of renal hypertension, masked by dietary restriction, can be restored by appropriate adrenal hormonal therapy. Even if little else has been established, essential hypertension is undoubtedly a familial disease with an onset relatively early in life. If it should be proven that renal hypertension is the result of a failure to

excrete rather than the excess production of a pressor substance, then it might be possible to integrate many isolated findings. For example, one might speculate that an unknown metabolite, acting on the arterioles or sensitizing them to some such substance as norepinephrine, is normally excreted and therefore present in too small concentration to do harm, that it is retained in renal disease, that it is produced in excess by an error of metabolism in essential hypertension; and that it is blocked at a renal or prerenal level, or influenced in some way, when an excess of adrenal cortical hormones is present.

The tempo of research has increased immeasurably in recent years and has emphasized among other things the role of psychological maladjustment and of stresses and strains of life in chronic and degenerative disease. The excitement of new developments, particularly in the realm of the synthesis of steroids, has opened entirely new fields of investigation and therapy There is an important place for both the investigator in the laboratory or clinic, as well as the practitioner with his unique opportunities for direct contact with the patient, for close observation, and for critical evaluation of the responses to therapy. However, both must preserve their scientific critiques and not permit themselves to be swayed too far afield by attractive but unsubstantiated theories For in the long run, only by careful fact-finding at a fundamental and then a clinical level, can we hope to find the solution to the many unanswered problems and help our patients who become ill

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Chapter 17

THE MEDICAL MANAGEMENT OF ACUTE AND CHRONIC ARTERIAL OCCLUSION *

A. Wilbur Duryee †

WITH THE EVOLUTIONARY changes in medicine of the past two to three decades, the medical man of today is faced with arteriosclerosis as the leading pathology of our age It is therefore natural that he will frequently be faced with the management of this disease as it affects the extremities. I use the term management in preference to treatment in that since the etiology of arteriosclerosis is still unsolved we therefore have no specific therapeutic approach

The purpose of this presentation is to analyze the available methods of management now in vogue and to attempt to outline a procedure that is both rational and most apt to produce satisfactory results. Many therapies have been developed and tried and while it is true that some of these apparently produce results when used by those who developed them and are familiar with their minute details, these same therapies fail when used generally.

There are those who make exorbitant claims for *specific modalities* of treatment and on the other hand those that feel that little can be done when arteriosclerosis blocks peripheral blood vessels. There must be a happy medium and a method of management which will effect an increasing blood supply to an extremity with arteries partially obliterated.

Tonight you are also going to hear from a surgeon who will outline his approach to this problem The fact that he is on this program should indicate that in this disease both medical and surgical methods of management should be considered The patient will benefit when a well-balanced team of a medical man and a surgeon cooperate—or when

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lowing information is of greatest value. It can only be obtained by an understanding of the pathology, a history, and a complete clinical and laboratory study.

Pathology

The vascular pathology in peripheral arteriosclerosis is most variable. You have listened to most excellent descriptions of these changes by

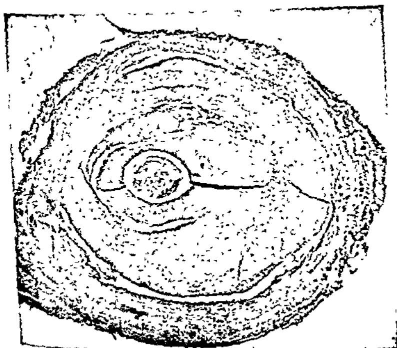


Figure 53 Marked atherosclerosis of the popliteal artery with narrowing of the lumen.

previous speakers on this Graduate Fortnight Program (1, 2) Smaller end arteries may be the site of most of the pathological changes or these vessels may be little involved and the main "shut-off" take place by a thrombosis in the major arterial supply in an extremity I shall not attempt to cover in detail the many variations noted but I would like to impress the point that there is *no* usual or set pattern of involvement.

The actual process in the wall of the vessel may consist simply of

either a medical man or a surgeon has a well-balanced insight into the specific case.

Analysis of the Problem

A set plan of management cannot be laid out which will fit each and every case of occlusive arterial disease. Every patient presents a different set of problems in his management, and these must be studied from both the general standpoint and from a proper analysis of the actual vascular changes in the extremity. I do not believe that all cases of peripheral arteriosclerosis should undergo a sympathectomy, as recently stated at a meeting of specialists in this field; nor do I believe that the use of a certain vasodilating drug is the therapy of choice.

From the general standpoint one must first consider the temperament of the individual. Is he the type who will cooperate in a conservative regime—who will relax while under treatment and who will accommodate himself to his limitations? If he is this type his prognosis is immediately improved.

Secondly are there associated vascular involvements that will make his management difficult? Particularly is there cerebral involvement to hamper his cooperation or to make it difficult for him to understand his problem? While a physician should not be too pessimistic to the patient about the outcome of his specific case, it is well to present the various possibilities and to especially emphasize the time factor in the course of this disease—one frequently losing the confidence of his patient if he tells him that a lesion should heal in a few weeks and instead takes several months to achieve the result or fails to heal.

There may also be associated disease independent of the vascular pathology. The patient may have diabetes, increasing the gravity of the vascular changes. He may have osteoarthritis making a long period of bed rest impossible or adding confusing symptoms, frequently mistaken for those secondary to his vascular disease. There may be disease of the spinal cord, blood dyscrasias, vitamin deficiencies, orthopedic defects, or any one of many less common diseases. The failures in the management of a vascular problem often result from the lack of recognition and proper treatment of the associated disease.

The analysis of the actual vascular status in the involved extremity is of utmost importance in arriving at a regime of management. The fol-

areas of a vessel may be involved with a relatively healthy wall remaining distal and proximal to the diseased area. For example, an arteriogram may show a site of occlusion in the femoral artery with collateral circulation filling a patient's femoral vessel below the occluded area (Figure 55). It is also episodic in its occurrence.



Figure 55. Arteriogram showing a thrombosis of the mid-portion of the femoral artery with excellent collateral circulation around the point of obstruction.

The degree of calcification as shown by x-ray, moreover, is not an indication of the degree of arterial impairment, and the failure to visualize calcium does not rule out arteriosclerosis as being present (Figure 56). Recanalization of a thrombosed vessel may occur, but such a healing process is rare and usually productive of little blood supply

One must also consider functional pathological changes in every case of impaired arterial supply In arteriosclerosis these changes are usually not marked in the early course of the disease, but when pain, especially rest pain, develops, then a reflex spastic state of the vessels with insufficient organic change to affect their ability to contract may take

soft or atheromatous changes or it may be associated with fibrosis and the deposition of calcium. Pathological changes of a degenerative and replacement nature may involve the media and leave the intima relatively normal. Reduction of blood supply in this type usually occurs as a result of the narrowing of the ostia of the branches of the arteries.

When intimal involvement takes place two chief changes are noted, first thickening and then thrombosis—many cases have a gradual narrowing of the vessel lumen while others superimpose a sudden thrombosis—even early in the course of the disease (Figures 53 and 54).

Peripheral arteriosclerosis is usually segmental in nature, that is, local

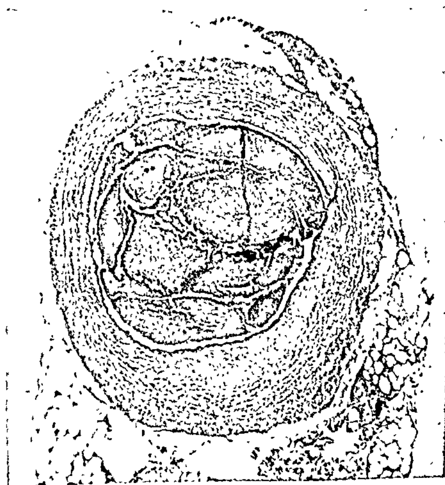


Figure 54. Atherosclerosis of posterior tibial artery with an acute thrombosis.

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place. This further reduces blood supply, and its control is the basis for much of the therapy advocated in the management of this disease.

Although the associated venous drainage is not usually affected to the same degree by organic changes in the walls of the veins, secondary venous thrombosis is common and complicates the arterial pathology. Such thrombosis probably occurs as a result of a reduced rate of blood

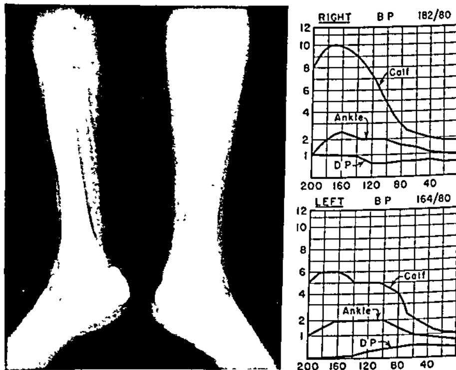


Figure 56 Normal oscillometric readings on lower extremities showing a very marked degree of calcification

flow, a reduced activity of the patient, and because many of these patients have associated varicose veins.

History

1. *Distress.* The patient with arterial insufficiency usually first complains of symptoms suggestive of intermittent claudication (3). These may come on gradually during a period of months or years or may be of acute onset. There is greater chance for the development of collateral

circulation in the slowly developing occlusion than in the case with a sudden arterial shut-off.

This extremity distress must be differentiated from pain secondary to spinal arthritis or other associated disease. Such pain is frequently present most of the time—aggravated, usually, at the start of activity and not relieved by the cessation of activity. Intermittent claudication moreover is not usually manifested by a true pain, but rather by a sense of tightening in the muscles and an inability to walk with almost immediate relief by the cessation of walking.

When arterial insufficiency has progressed to a point where pain is present at rest, such pain is usually severe, more apt to occur after the patient has gone to sleep and relieved by placing the extremity in the dependent position.

2. *Temperature changes*, especially coldness, occur with both organic and functional arterial disease and more frequently are an indication of vasospasm than of organic occlusion. However, when one extremity is cooler than the other then organic occlusion is more likely responsible for the reduction in skin temperature.

3. *Slow nail growth* with transverse ridging of the nails indicates periods of reduced nail bed blood supply.

4. *Night cramps* are usually an indication of venous stasis and not of arterial insufficiency. They should be differentiated from night rest pain which is usually not associated with muscle cramps.

As one can see, there are not many symptoms related to peripheral arterial insufficiency and the disease may progress to a considerable degree before the patient is aware of his difficulty. It also goes without saying that a most complete general history should be recorded from each patient.

Physical Examination

A complete examination is of utmost importance. Everyone is aware that the arterial supply to the extremities is altered by many factors besides local pathology. The pulse in an extremity of a patient with systolic hypertension and aortic insufficiency is bound to be much different than in a patient without valvular defects and with a marked hypotension. Aside from the vascular system, endocrine disturbances, malignancies,

and maldevelopments may account for impaired arterial supply. These are only a few examples of conditions one must be on the lookout for in the general examination.

Extremities should be examined comparatively in the horizontal, dependent, and elevated positions. The cardinal signs of rubor on dependency and pallor on elevation can only be noted with such postural changes. Trophic changes of skin, muscle, and subcutaneous tissue as well as nail and hair growth should be observed and the two corresponding extremities compared. Temperature changes by palpation at various levels of an extremity should be noted and compared to the opposite extremity. Measurements should be made at corresponding levels and pulses should be palpated at accessible locations; in the upper extremity —in the axilla, antecubital area, and at the wrist on the ulnar and radial sides, in the lower extremity—at the groin, popliteal space, behind the internal malleolus, and over the dorsum of the foot. The abdomen should be examined for iliac or aortic pulsations when femoral pulsations are not felt.

Although the diagnosis of occlusive arterial disease should be made by a careful history and physical examination, certain laboratory aids are indicated in each diagnostic workup. A urine analysis, complete blood count, sedimentation rate, hematocrit, blood sugar, and Wassermann are basic. Other tests may be done if indicated. An x-ray of the extremities showing calcification of arterial walls aids in the diagnosis of arteriosclerosis—a normal film does not eliminate this disease process. Specialized procedures must be applied as indicated but are not a necessity in every routine study The two most valuable aids are oscillometric studies and vasodilatation tests. They both may be misleading, and like any other diagnostic procedure their interpretation in view of other clinical and laboratory findings is important.

The oscillometer may give positive information where the palpating finger fails to do so. It may locate pulsations missed otherwise. It is of value in comparing corresponding areas of extremities and in noting changes following vasodilatation tests. However, comparison readings are useless unless the patient is examined under the same basic conditions and in the same position. Blood pressure should be noted at each testing period. The method of application of the cuff may alter the readings

and variations of the amount of subcutaneous tissue affect the degree of pulsation

Vasodilatation tests of many types have been described. The original test of measuring peripheral skin temperature following the induction of elevated body temperature by the intravenous use of typhoid vaccine gave a very good estimation of the vasomotor index (4). Reflex methods of inducing peripheral vasodilatation are easier on the patient and give satisfactory results. Paravertebral nerve blocks give a more rapid method of testing, but there is always the possibility of an unsatisfactory block. They do, however, usually permit a comparison study of the two sides. Caudal anesthesia is of value in eliminating vasospasm bilaterally and of the distal parts of the extremities Spinal anesthesia gives a higher level of vasodilatation but may drop blood pressure to a degree where it affects peripheral blood flow. The sympathetic blocking agents unless injected intra-arterially are of little assistance because of their generalized action.

In summarizing these vasodilating procedures I believe it wise to rely on more than one method in studying any specific case, particularly if the results of one test do not fit the clinical picture

In interpreting the results of such tests various criteria have been suggested—originally (4) a rise of 6° F was thought to be necessary if satisfactory results from a sympathectomy were to be expected. More recently some surgeons have gone so far as to state that even when there is no rise in peripheral skin temperature following such procedures, satisfactory clinical results can be obtained from *division* of the sympathetic preganglionic fibers. I personally believe that a clear-cut rise of from 2 to 4° F *must* result from these tests in order to expect improvement from vasodilatation procedures The degree of rise will depend on such factors as the temperature level of the control period, the duration of the test, the relaxation of the patient, as well as on the relative vasospastic and organic changes in each case

One could detail numerous other tests devised to measure the degree of circulation in an extremity, but such is not the purpose of this paper. They play only a small role in evaluating each case Aortograms, arteriograms, various circulation time studies, especially the fluorescein test, the use of isotopes, and methods of measuring claudication are all helpful

but as a rule complicated and not necessary in the evaluation of the usual case of peripheral arteriosclerosis.

Management

When one has thoroughly studied a specific case of occlusive arterial disease he must plan a regime of management to fit that case—such a program may have to be intensive and emergency in nature where the shut-off has been sudden or rapid in its development and it may be conservative in the slowly developing process of occlusion. In the latter case adequate collateral circulation frequently develops spontaneously so that the patient notices improvement without therapy. Moreover, if the problem is complicated by other vascular manifestations or other disease a more detailed outline of management will be necessary.

While many of you listening to this presentation may be expecting the description of some new procedure or the details of the use of some new drug, I shall have to disappoint you In the remaining part of this discussion I shall attempt to discuss the various modalities of available therapy and to evaluate each in proper aspect to the others in a regime of management. In any one case four main factors determine the outcome. First, can the primary process be arrested? Second, can collateral circulation be developed to an adequate degree before the main blood supply is occluded? Third, can infection and trauma be prevented in the tissues with deficient blood supply? And fourth, what means can be utilized to prevent thrombosis? In the first instance I know of no method of arresting the progression of occlusive arteriosclerosis as can be done in thromboangiitis obliterans where the cessation of the use of tobacco appears to stop the progress of this occlusive disease Proper diet may have some effect in delaying its progress. A better understanding of the metabolism of cholesterol and the lipoproteins is leading us to eliminate certain fats. Lipotropic substances may play a role in averting this disease, but recent papers are not too encouraging from this standpoint. In the second, third, and fourth instances a program of management is developed in an attempt to accomplish these results, i.e., increase collateral circulation and prevent infection and trauma and thrombosis. In order to accomplish these aims certain basic principles of management must be understood and correctly applied

Rest versus activity. In the acute or far-advanced occlusive process with

rest pain, rest is imperative almost as much so as in the patient with an arterial shut-off to the myocardium. It must be complete as far as walking is concerned, until all vascular rest pain has cleared. However, when the process is early and in cases without rest pain then use of the extremities within their vascular capacity is the best method of stimulating collateral circulation. Activity, however, must be limited to that possible without the production of intermittent claudication Once this symptom has occurred vasospasm of the normal or relatively normal vessels probably takes place leading to further thrombosis. It is not an uncommon story that a person develops an acute exacerbation of his pathology after trying to force walking against claudication symptoms. Train your patient to walk slowly and walk frequently but to limit his distances to those he can do without distress. Many patients can walk three to four times as far at 90 steps per minute than they can at the usual 120 steps per minute (5). They can walk further on the level than up inclines, or when not burdened by carrying heavy objects Their claudication distance is less on hard pavement than on turf

Temperature. Various extremes of local environmental temperature have been advocated in the management of occlusive arterial disease. Originally high temperatures induced by infrared lamps, heated cradles, and diathermy or short wave were applied to stimulate circulation. It was soon noted that with such elevated temperature levels, burns, gangrene, and deep tissue necrosis occurred and on careful study it was shown that with impaired arterial supply the increased metabolic needs of the tissues could not be met. The pendulum then swung to the opposite direction and extremely low temperatures were used. These were found also to be detrimental as they induced vasospasm and occasionally gangrene by freezing Today we believe that average room temperature is probably the most logical level, but that self-generated heat should be maintained by soft nonconstricting warm protective padding, clothing, or covers.

Position of extremities. An optimum position of the extremities with arterial impairment on an organic basis is most necessary. All too frequently extremities with impending or actual gangrene have been elevated above heart level adding to the ischemic state of the tissues by drawing the blood from inelastic vessels On the other hand the patient himself frequently indicates the logical position by dropping his legs over the side of the bed in order to get relief from his rest pain In severe

cases the patient may sleep in a chair in order to rest at night. However, he usually overdoes this factor by keeping the legs dependent too long and increasing venous and lymphatic stasis, thereby complicating the problem.

The most ideal position is probably one with the extremities somewhat below heart level (6). This can be accomplished by elevating the head of the bed on shock blocks, the degree being determined by several observations. In cases with severely impaired circulation and no venous or lymphatic disease, a fairly marked dependency should be used. When varicosities are present then less marked dependency or even a level position may be optimum. Any position producing edema or marked rubor or cyanosis is too low, and any position producing pallor is too high.

Protection of extremities. I shall mention this angle but briefly although it is very important. In skin with impaired arterial supply even slight trauma, mechanical, thermal, or chemical, may precipitate necrosis. One must be particularly careful of heel pressure in a patient confined to bed. Sunlight and artificial ultraviolet, strong antiseptics, and the application of acids must be avoided.

Avoidance and treatment of infections. Many cases of gangrene develop as a result of infection. Tissue destruction may be the result of fungus or bacterial invasion. Following poor chiropody a break in the tissue at nail margins or in the area of calluses may be the portal of entry for bacteria. A fungus infection of the skin, benign and unnoticed in the webbing between the toes, often is the original site of gangrene (7). Therefore careful hygiene of the skin with daily soap and water baths followed by careful drying between the toes is of utmost importance If a fungus is present or suspected daily soaks in a mild fungicide solution such as 1 to 5000 potassium permanganate are indicated. The toes should be separated by some small firm objects during the soaks to permit the solution to come in contact with the web areas. In addition some of the mild fungicide powders should be used twice a day between the toes and in the shoes, especially if there is much sweating of the feet. Such therapy should be given both feet If there is any allergic response to these medications, they should be immediately discontinued because the resulting skin lesions may become sites for infection.

Bacterial infection should be treated early and intensively. Locally, careful, frequent debridement of the area should be done to expose all of the involved area to the air. Only dead tissue should be removed Ointments covering infected areas should be applied sparingly and with a water-soluble base and not with an oily base. They should be removed daily and replaced. In many instances, normal saline compresses to keep the tissue soft and to avoid crusting are the applications of choice, and each individual needs careful watching with solutions applied only long enough to accomplish this without causing necrosis. When infection has been controlled, then tissues should be left dry and dead tissue allowed to separate from healthy tissue

Antiseptics and antibiotics are seldom of value when used locally; their oral or parenteral use is indicated provided local skin reactions do not result. For this reason penicillin must be used with caution. The blood levels should be high since with deficient local blood supply the involved area will not receive adequate amounts of the agent Those antibiotics which may be used intravenously have been injected into the arterial supply of the involved extremity when the major vessels are patent, in this way getting a greater concentration of the agent to the desired area

One word of precaution should be given regarding the possibility of the mold types of antibiotics activating an underlying fungus infection. If such occurs they should be discontinued or adequate fungicidal therapy used coincidentally. The sulfa preparations may be found to be safer and as effective as the mold group of antibiotics

Elimination of factors that reduce blood supply It is apparent that all mechanical factors, that by pressure on blood vessels impair circulation, should be eliminated In addition vasospastic substances should be avoided. Tobacco being a marked vasoconstrictor should be completely eliminated and such drugs as Adrenalin, epinephrine, and ergot avoided. Pain can cause a high degree of reflex vasospasm and its control is a major problem in the management of these cases Opiates give little relief from the pain of vascular gangrene and because of the long duration of therapy their use should be kept at a minimum Many of the procedures already outlined will reduce the pain factor, and of all drug therapy, the use of alcohol in the form of whiskey or brandy together

with salicylates seems to produce the best analgesia. One ounce of whiskey and 10 gr of aspirin often will relieve ischemic pain as well as morphine or other narcotics.

Intravenous procaine has been advocated as a vasodilator. However, I believe that its chief effect is that of an analgesic and that any vasodilation accomplished is done by eliminating vasospasm secondary to pain.

Vasodilatation. I approach this part of the regime with some misgivings. Various workers have described innumerable procedures to accomplish this all-important process. Physiotherapy, drugs, mechanical appliances, and surgery have all been advocated and used alone or together. I would like to emphasize that one should rarely depend on a single modality alone. If I should attempt to analyze each procedure or drug it would take many hours. I shall therefore try to give you my present concept of certain general procedures of value in increasing peripheral vasodilatation. There are two reasons to increase blood supply. First, to supply the muscles with more blood in order that walking distances may be increased and, secondly, to increase blood supply to the skin to maintain its integrity. Although there is some dispute regarding the sympathetic innervation of these two blood supplies it is more commonly believed that the sympathetic control is most marked to the skin vessels and that muscle blood supply is not affected to any degree by sympathetic nerve blocking. It is my clinical impression, and such is largely substantiated by numerous workers, that little can be done from a vasodilatation standpoint to increase blood supply to the muscles and that we must depend on the use of these muscles as a stimulus for the development of collateral circulation.

However, the usual total disability of a patient with peripheral arteriosclerosis starts with tissue breakdown in the skin and here vasodilatation can be frequently accomplished to a most satisfactory degree. The warm dry skin after a lumbar sympathectomy is proof of this.

From a medical standpoint, numerous orally or parenterally administered, so-called vasodilating drugs have been developed and used in the management of occlusive arterial disease. Some of these have been claimed to have a more pronounced effect on the sympathetic supply to the lower extremities than to that of the upper extremities. Within the last two years many investigators have reported that such therapy not

only is frequently valueless but more often tends to rob the involved extremity of its total blood supply in order to fill dilated healthy vessels in other parts of the body (8). There are still many that do not agree with this statement. There are also other reasons for not using these drugs systemically since annoying side effects from visceral action often prevent their use and drops in blood pressure interfere with their value.

If vasodilatation is to be obtained from drug therapy it should be the result of the application of the drug so that its maximum effect is to the blood vessels in the involved extremity. Thus procaine injected paravertebrally blocks the sympathetic supply to the desired general area. The same is true of the intra-arterial use of drugs such as histamine (9), Priscoline, and Etamon. Mecholyl may be used to promote local vasodilation in limited areas by applying it through the principle of iontophoresis (10).

Mechanical therapy. Various types of apparatus, such as the oscillating bed, suction pressure boot, and intermittent venous occlusion apparatus have been developed to assist in the management of occlusive arterial disease. The various types of oscillating beds probably have the greatest value in that they utilize gravity to fill and drain partially obstructed arteries with stiffened walls. Gravity with the extremity dependent may also force some vasodilatation to add to this effect. However, their value has been clearly demonstrated. In order to accomplish satisfactory results, these beds should be so constructed that the patient is comfortable, that they operate quietly, and are easy of adjustment. This latter quality is essential as a bed must be capable of being adjusted to the requirement of each individual. The period of elevation should be just long enough to produce a slight blanching and the period of depression sufficient to allow good filling of all vessels with the accompanying state of rubor as evidence.

Intermittent venous occlusion is said to work on the principle that if the venous return is occluded for a period and then released that during the period of free flow more arterial inflow takes place as a compensating mechanism and that this is accomplished through a reflex vasodilatation. Diligent workers in this field claim good results from this procedure although there are many that feel that the clinical results are doubtful.

Suction pressure apparatus was one of the early forms used in the treatment of impaired circulation to an extremity. Its principle is sound

but its application difficult, and therefore this procedure has largely been discontinued. For its success there must be adequate major vessel supply distal to the retaining cuff, the cuff must fit snugly but not tight enough to act as a tourniquet, and rather constant attention by a technician is necessary to keep the operating conditions satisfactory. The periods of pressure and suction and the degree of each should be adjustable and fitted to each case.

Another method of physiotherapeutically handling this problem is by the utilization of reflex heat. Placing the arms in hot water, using heat pads on the body or heating the abdomen with various types of electric wave therapy are sound procedures to produce vasodilatation.

Anticoagulants. If thrombosis in the arterial tree can be prevented and complicating venous thrombosis avoided then we have accomplished a great deal in giving collateral circulation a chance to develop. By promoting as rapid a blood flow as possible, avoiding periods of vasospasm, avoiding trauma, and by maintaining hydration the tendency for thrombosis is reduced. Blood dyscrasias, especially polycythemia, must be recognized and coincidentally treated

With the available anticoagulants we also have a means of handling this problem. I doubt if every case of peripheral arteriosclerosis should be given an anticoagulant, but I do believe that all acute arterial thromboses (and emboli) should receive a combined heparin-Dicumarol regime and that such a regime should be continued until the patient is ambulatory. Patients put to bed for several weeks' bed care because of impending gangrene should receive anticoagulant therapy especially as a prophylaxis against venous thrombosis, which would complicate the local problem and be a possible site of pulmonary embolization.

In the acute case heparin should be given, preferably in saline form, subcutaneously, every 3 hours in doses adequate to double or triple the control clotting time. When the coincidentally administered coumarin derivative (Tromexan, Dicumarol, etc) has elevated the prothrombin time to 2 or 2½ times its normal level, the heparin is discontinued Initial doses of Dicumarol average 300 mg and of Tromexin 1500 mg followed by daily doses of one-half or one-third or less of the initial dose. Daily prothrombin times are a must Some investigators have advocated much larger initial doses to be followed by a smaller dose days later when the prothrombin time begins to drop.

Accessory general therapy should not be overlooked. Tissues with im-

paired blood supply receive deficient amounts of food substances and vitamins. The diet therefore should be high in protein and in sugar (if no diabetes is present) and accessory vitamins added. Vitamin C in large doses is necessary to maintain capillary wall integrity and vitamin B complex for its effect on nerve nutrition.

Obesity must be corrected by regulating the calorie intake. Endocrine deficiencies should not be overlooked as a patient with hypothyroidism needs thyroid to increase the circulation rate The vasomotor instability of the climacteric period should be controlled by the proper doses of estrogens or androgens.

While Dr. Lord (11), who will follow me tonight, will go into the surgical aspects of this problem you might like to hear a medical man's brief opinions of some of the surgical procedures. These are as follows.

Sympathectomy should be utilized in patients needing increased blood supply to the skin of extremities with gangrene or symptoms of marked ischemia. Such patients should show a vasospastic state with an ability to vasodilate. It is not a method of treating intermittent claudication and it will not reverse the process of arteriosclerosis as one outstanding surgeon has stated.

Aneurysms, involving arteriosclerotic vessels in the periphery, should be surgically treated.

In cases of localized thrombosis of major arteries associated with a marked vasospastic state arteriectomy is indicated The possible use of an autogenous vein transplant or the use of an arterial segment from a bank must be considered in locally occluded areas

Amputation should not be delayed where it is evident that a gangrenous process is extending and cannot be controlled by the above medical and surgical procedures

Summary

One may ask how he is to determine which of the above procedures to utilize in the management of an individual case. Such choice of a regime must depend on a careful study of the problem. On one extreme simply the proper use of the legs with general advice as to the care of the extremity may be entirely adequate. On the other hand acute or advanced cases need hospital care with the application of as many of the discussed procedures as are available and can be easily correlated.

I would like to stress the point that it is extremely difficult to evaluate

any one procedure in the management of occlusive arterial disease. As already stated spontaneous improvement frequently occurs as collateral circulation develops and too frequently some modality of therapy is given credit. This fact would perhaps account for the numerous methods which have been advocated in the control of this disease process.

Conclusions

1. The patient must be treated and not alone his extremity.
2. A proper understanding of the underlying pathology is important.
3. Each case must be thoroughly studied before a regime is outlined.
4. Cooperation between the medical man and the surgeon is important.
5. The successful management of each case depends on the outlining of a regime embodying the indicated modalities of therapy.
6. Drug therapy, from the vasodilating standpoint, plays only a small role in the management of most cases.
7. The more acute or advanced the process the more intensive the regime should be, many cases needing hospital care.
8. The regime for each case should include the treatment of associated problems such as arthritis and obesity.
9. The prognosis of this disease is not as grave as it was once thought to be.

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Chapter 18

THE SURGICAL THERAPY OF ACUTE AND CHRONIC ARTERIAL OCCLUSION *

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THE THERAPY of acute arterial occlusion is determined not only by the pathogenesis of the arterial block, but also by the setting in which the episode takes place. As is so often the case, proper therapy rests squarely on an accurate diagnosis which must be made as a rule by the clinical appraisal of the patient.

In general, there are four causes for a sudden block in an artery: 1) embolic, 2) thrombotic, 3) traumatic, 4) spasmodic. Let us consider briefly each of these causes.

An embolic occlusion of an artery may have had its origin in the left auricular appendage of a patient suffering from mitral stenosis and chronic auricular fibrillation, usually an individual under fifty years of age, predominantly female. The second group of patients who may embolize from their hearts are those with myocardial infarction and an associated mural thrombus This group is usually beyond fifty and predominantly male Finally, an occasional patient will manifest an embolic episode from a thrombus originating in an arteriosclerotic abdominal aorta or from an aneurysmal sac. The second important cause of an acute arterial occlusion is the thrombotic episode occurring suddenly in an individual with an advanced arteriosclerotic process in which an intimal plaque has ulcerated and served as the nidus for thrombus formation and blockage of the arterial blood flow Usually these patients are above fifty and manifest generalized arteriosclerosis. An accurate differential diagnosis between an acute thrombotic occlusion and an embolic process may be impossible in some patients of this type. Thirdly,

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the traumatic occlusion of an artery may occur as a result of a bullet, knife wound, fracture with laceration of the vessel, or may occur in the operating room usually as a result of a surgical error, although occasionally the artery may be deliberately ligated for purposes of resection of a malignant tumor. Diagnosis in this group is usually simple providing the peripheral pulses are carefully palpated in the involved as well as in the normal extremity. Finally, an acute arterial occlusion may be entirely on a spasmodic basis which in some cases may simulate an organic block and can be equally disastrous. One of the clearest examples of this type of spasmodic block of an artery is seen in the acute massive venous occlusion so ably described by Haimovici (1) and Veal and his associates (2).

The therapeutic management of an arterial occlusion may be operative or nonoperative depending on the diagnosis and other related factors. In Group I, the embolic cases, ideally an embolectomy should be performed in the younger patients (under 50) if seen within ten hours of onset, if the artery obstructed is the aorta, iliac, or femoral artery, and if the general condition of the patient is such that an operative procedure is tolerable The comprehensive management of such a patient follows

V. McC., a 44-year-old white woman, was a known rheumatic with mitral stenosis and auricular fibrillation and had been subject to several bouts of cardiac decompensation On January 25, 1951, she suddenly experienced paralysis of the legs followed shortly by low back and upper thigh pain Dr William T Foley saw her within one hour of onset, diagnosed a saddle embolus of the aorta (no femoral pulses, cold, white legs, and absent sensation in the feet), and admitted her to the New York Hospital In addition to the aortic embolus, pulmonary edema had developed This was managed by a supplementary dose of digitalis, aminophylline, oxygen, and morphine Under continuous spinal anesthesia, which has the multiple benefits of abolishment of the sympathetic tonus to the lower extremities, and contracting the intestines with relaxation of the abdominal musculature, the aortic bifurcation was exposed through a left rectus muscle-splitting incision Following the isolation of the aorta and the common iliac arteries, an arteriotomy was made in the right common iliac artery within 1 cm of its origin The embolus was removed, the incision in the artery closed with an everting mattress suture of 5-zero silk, and the posterior peritoneum carefully closed over the vessels Recovery was satisfactory, the patient being discharged from the hospital on the seventeenth postoperative day in good condition Two months later, catheterization studies were performed by Drs. Charles T. Dotter and Daniel S Lukas The findings were in keeping with a

tight mitral stenosis. Therefore, on April 14, 1951, a left auricular appendectomy and commissurotomy were carried out with an excellent clinical result The salient pre- and postoperative catheterization data are shown in Figure 57. In suitable patients with mitral stenosis, auricular fibrillation, and embolic phenomenon, it would seem desirable to attack not only the embolus but also to rid the patient of the source of the embolus, usually the left auricular appendage.

In general, the contraindications to an embolectomy are· 1) patients with emboli to the upper extremity and those in the lower extremity from the popliteal artery down. Occlusion of an artery in the upper ex-

	Preoperative	*Postoperative*
Cardiac Output		
L/min		
Rest	3.78	4 57
Exercise	3 73	4.95
Pulmonary Artery		
Mm Hg		
Rest	57 — 24	45 — 21
Exercise	76 — 39	74 — 34
Pulmonary Capillary		
Mm Hg		
Rest	26	18
Exercise	34	32
Mitral valve area in cm²	0 70	2.35

Figure 57. Cardiac Catheterization. (V McC, 44 yrs., f.)

tremity seldom causes gangrene because of the rich collateral circulation, while a block in the popliteal artery is usually associated with operative technical difficulties which outweigh the usual values of operative over nonoperative management, which Dr. Wilbur Duryee has discussed in his presentation. 2) The age of the patient and his associated arteriosclerotic process make unwise an operative removal of the embolus in the elderly for two reasons First, the vessel is often sclerotic to a degree which predisposes to thrombosis postarteriotomy, and, secondly, there has usually been *pari passu* with the arteriosclerotic process an increment in the efficacy of the collateral circulation so that sudden occlusion of the main artery may be better tolerated 3) When the time lag between the

onset of the embolus and the operation is such that early irreversible changes in the foot are present or local changes of adherence of the embolus to the vessel wall may lead to thrombosis following arteriotomy due to endothelial damage. The recent development of regional heparinization by Freeman, Wylie, and their associates (3, 4) broadens the indications for embolectomy as far as the age and time factors go. A polythene catheter is introduced into the artery above the arteriotomy incision and 50 mg of heparin in 500 cc of 5 per cent glucose in water is allowed to run over a period of twelve to twenty-four hours Heparinization may be continued for one to five or six days by this method without seriously altering the general clotting time. 4) The general condition of the patient including his cardiac status may preclude an operative procedure as too great a risk to life.

The ideal management of the patient with an acute thrombotic occlusion of a main artery is still conservative or nonoperative. Thrombectomies with regional heparinization may occasionally be successful but are usually surgical exercises, and the loss of life due to operative intervention probably overrides the infrequent success following surgical intervention under such circumstances. Fortunately, nonoperative methods will lead to a favorable outcome in the majority of instances

Acute arterial occlusion due to trauma occurs with sufficient frequency to merit planned consideration of its management which is successful in a high percentage of cases. Whether the injury to the artery has occurred, on the one hand, in the street, in an industrial accident, or due to violence or, on the other, during a procedure in the operating room, time is the most important factor. From two to twelve hours is the golden period for repair of an arterial injury. The ideal in management is prompt arterial repair by direct suture or by an autogenous vein graft or a homologous arterial graft. Arteries which have been ligated during an aseptic operative procedure such as a hernioplasty or during a high saphenous ligation may well be reconstructed twelve to twenty-four hours following closure of the wound with a high expectancy of success

The spasmotic type of acute arterial occlusion seen most frequently in massive venous thrombosis of the lower extremity is handled best by Veal's method of vigorous passive and active exercise of the leg with marked elevation as soon after the onset as possible The arterial spasm is relieved as soon as the venous block has cleared, usually a matter of

one or two hours or less. Previously we have managed several cases satisfactorily by venous thrombectomy of the superficial femoral vein under spinal anesthesia followed by anticoagulants, elevation of the foot of the bed, and massive warm compresses to the leg. However, Veal's method (2) is so much simpler that it warrants a thorough trial in this group of cases. Occasionally, spasmotic occlusion of an artery will follow a fracture or dislocation of a joint which is in close proximity to the vessel. A paravertebral or stellate ganglion procaine block and anticoagulants will usually suffice to abolish the arterial spasm following correction of the fracture or dislocation.

The surgical therapy of chronic arterial occlusion should, in my opinion, be limited to carefully selected cases, usually after a thorough trial with nonoperative measures. In the surgeon's armamentarium there are several procedures which have been explored during the last five years, but only one seems to have a real therapeutic effect in properly selected cases, namely sympathectomy. When this operation is carried out indiscriminately and routinely on patients with chronic arteriosclerotic and thromboangiitic occlusive disease of the lower extremities, it has been disappointing and frequently without value. Conversely, in patients with *demonstrable* vasomotor tone of greater or lesser degree, then sympathectomy may effect a beneficial change sufficient to warrant its use. Both on the Fourth Surgical Division at Bellevue Hospital and in private practice, a good result following sympathectomy has rarely evolved when preliminary tests have shown no evidence of vasomotor tone. When possible, we have employed the cool environment of a constant temperature room at 68° F and have carried out a paravertebral block with 40 cc of 1 per cent procaine. If a temperature rise in the toes was detectable or if a cyanotic hue changed to pink or if constricted veins over the dorsum of the foot became full, then we have evidence of some vasomotor activity. If the procaine block has not produced any objective change, then the patient is subjected to reflex heat, either by immersion of the hands and forearms in warm water or by a heating pad to the abdomen. Should any of the above changes occur in the foot, then we know that there is some vasomotor activity and that the procaine block was ineffectual. A sympathectomy, therefore, will be of value. On the other hand, when no objective change has occurred with either maneuver, then a sympathectomy is clearly contraindicated.

Another situation where sympathectomy is useless is in the patient whose only complaint is intermittent claudication. Silbert and his associates (5), Elkin and Cooper (6), and others have shown that sympathetic nerve block and sympathectomy do not increase muscle blood flow, in fact, may actually decrease it. Certainly the patient who would benefit from a sympathectomy because of skin changes in the foot or toes should not be deprived of the operation because of an associated intermittent claudication, but it should be clear to the patient and the physician that no improvement in walking distance will result per se from the sympathectomy.

Let us examine some of the other new and revived operative procedures discussed in the current literature as having value in the management of chronic arteriosclerotic occlusive disease One of these, the so-called revascularization of the leg by the production of a three-limbed arteriovenous fistula, has recently received favorable comment by Johnston and his associates (7), and by Ruggiero and Winfield (8). From 1900 to 1915, several reports were made about its possible effect on the circulation to the lower extremity, and Bernheim (9) reported the follow-up of one patient in 1931 who had been subjected to quadrilateral arteriovenous fistula with prolonged (18 years) improvement. The principle underlying the use of this procedure is that the femoral vein can act as an artery supplying blood to the capillaries when the main artery has been occluded. It has been conjectured that the reversal in flow through the vein will lead to utilization of oxygen by the tissues as a result of reversal of flow through the capillaries Several obvious defects are apparent, the solution of which may well be impossible. First, the venous valves offer either a temporary or permanent block to the reversed flow of blood and hence possibly to thrombosis. Secondly, the branches of the vein distal to its anastomosis to the artery may afford short-circuiting by-passes for the blood to return to the heart without reaching the peripheral capillaries. Thirdly, no evidence has been presented in either clinical or experimental material of an increased utilization of oxygen by the tissues of the distal parts of the extremity. Recently, Skinner and Parsons (10) reported on eight patients in whom they constructed a fistula in the femoral vessels of ten extremities with impending or frank gangrene in seven patients with arteriosclerotic occlusive vascular disease with and without diabetes, and one with

thromboangiitis obliterans. They found the operation to be of questionable value in only four limbs. Our experience with the procedure has been limited to some eight patients and in all but two it was of no avail. One patient has been lost to follow-up after three months of observation, and the single good result was obtained slowly over several months by averting frank gangrene in a 66-year-old man with impending gangrene of his toes and distal half of the foot. Six months later, a lumbar sympathectomy relieved the pain which had persisted in his toes. On the basis of the above experiences supplemented by unpublished data, one might safely conclude that the operation of creating a three-limbed arteriovenous fistula between the femoral artery and vein is one of dubious value and will need the presentation of further favorable experience with it before accepting the operation as an adjunct in the care of the patient with chronic occlusive arterial disease.

The operation of "scraping" the thrombosed artery, leaving a shell of media and adventitia, has been popularized by Bazy (11). The procedure includes isolation of the thrombosed artery from the point of occlusion distally as far as possible—usually the lower end of the popliteal artery, preservation of its branches, longitudinal incision throughout the length of the exposed artery, scraping the thrombus with the adherent intima from the lumen, then suturing of the entire arterial incision. During the operation and postoperatively for two to four days continuous anticoagulant therapy with heparin is necessary. Several unpublished studies have been made and some favorable results observed. We have carried out the procedure only three times but with disastrous results, one patient dying on the fourth postoperative day from hemorrhage and shock due to the heparin therapy, while the other two rethrombosed their arteries in three to six days. The operation is tedious and has the basic weakness of the fact that the arteriosclerotic process is usually extensive and progressive. Wylie and his associates (12) recently reported favorably on an improved technique, using fascia lata and regional heparinization in some cases This method is certainly the most promising one to be devised for the thrombotic group of patients.

A third operative procedure which seems likely of greater successful application, although suitable cases are in the minority, is the resection of a relatively short segment of the thrombosed artery followed by insertion of an autogenous vein graft thereby effecting restoration of

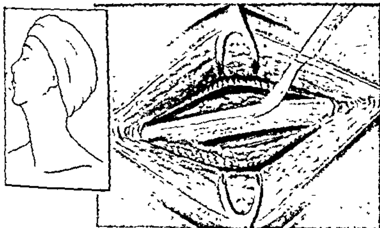


Figure 58 (*Left*) Skin incision; (*right*) incising periosteum to expose clavicle

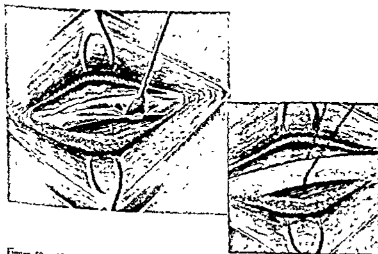
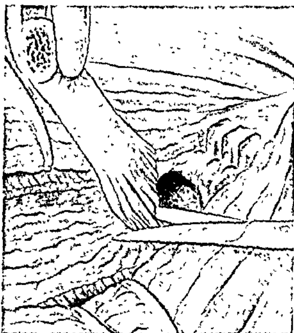
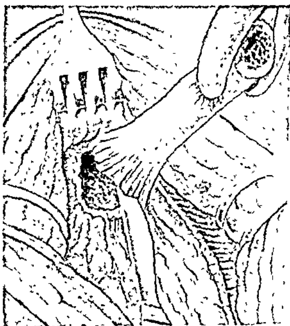


Figure 59. (*Left*) Reflection of periosteum from clavicle, subclavius muscle (*F*). (*Right*) Section of clavicle with Gigli saw.

blood flow through the main arterial channel. Holden (13) described such a case with a satisfactory follow-up of four months. We had one clinically ideal patient of 61 years in whom the arteriogram revealed a thrombosed 3-in. segment of femoral artery in the middle third of the thigh. Moderately severe claudication had been the only complaint, and a lumbar sympathectomy performed seven months earlier had been


Figure 60 Removal of lateral segment of clavicle.


Figure 61. Removal of medial segment of clavicle

without influence on the patient's walking distance. The thrombosed arterial segment was excised and replaced by a vein graft from the accompanying femoral vein. The lumina of the proximal and distal arterial segments were cresenteric due to marked plaque formation. Postoperative anticoagulant therapy was discontinued after four weeks. The posterior tibial artery pulsated well for six weeks, whereupon it abruptly disappeared, suggesting a fresh thrombosis of one of the anastomoses or

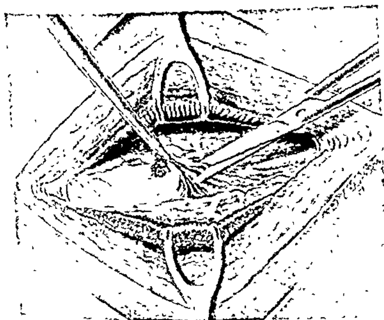


Figure 62. Excision of periosteum from clavicle bed

possibly elsewhere in the arteriosclerotic artery. Follow-up for five months shows that the patient's condition remains unimproved. Only with further experience will we be able to evaluate the operation described above. The patient stands little to lose because of the relative safety of the operation, but the important question is in what percentage will the procedure be successful.

Finally, the operation of arteriectomy has many proponents such as Leriche (14), Schnayerson (15), and others It is based on the principle that a thrombosed segment of artery serves as the stimulus of the afferent

are to cause vasoconstriction through the sympathetics at local levels not affected by lumbar sympathetic ganglionectomy. There is no group of patients more difficult to evaluate a form of therapy than those with chronic arterial occlusion, and, therefore, the efficacy of arteriectomy is hard to judge. In three patients in which we have carried out this operation, no improvement was observed.

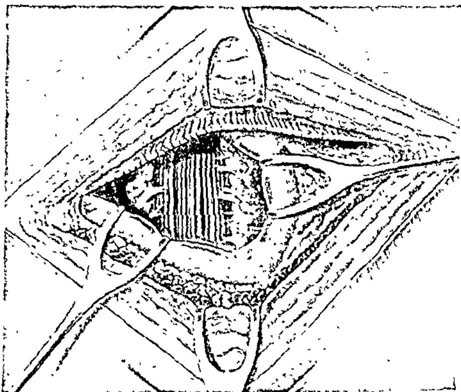


Figure 63 Exposure of scalenus anterior muscle and phrenic nerve.

Before closing, I would like to describe an operative procedure which, as far as I can determine, is a new approach to an interesting group of patients suffering from temporary and sometimes permanent occlusion of the subclavian or axillary artery due to one or more of the shoulder-girdle syndromes. This procedure was evolved by Drs. Irving S. Wright and Robert Huebner and the author in a group of eight patients suffering from a combination of two or more of the following syndromes hyperabduction, scalenus anticus, costoclavicular, with or without a cervical

rib Four of the patients had experienced complete occlusion of the axillary or subclavian artery after a period of intermittent occlusion associated with varying positions of the shoulder girdle and the arm, whereas the remaining four had exhibited only intermittent occlusion. In four of the eight patients, the condition was bilateral, two showing

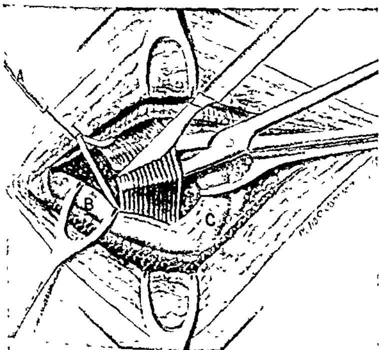


Figure 64 Scalenus anterior muscle sectioned Phrenic nerve (*A*), subclavian vein (B), external jugular vein retracted (C)

bilateral occlusion while in the remaining two it was intermittent. Only one of the eight showed Raynaud's phenomenon. The reader is referred to an excellent review by Beyer and Wright (16) for a discussion of the diagnosis and nonoperative therapy.

The operative procedure consists in total subperiosteal resection of the clavicle followed by removal of the periosteum, division of the scalenus anticus muscle, and mobilization of the subclavian artery (Figures 58–65) The results *in* eight patients with twelve involved upper extremities has been uniformly excellent in the follow-up of two to

fifteen months. In those without thromboses, the radial pulse is stroı *in all positions of the arms and in those with thromboses, radial pulsatic* has returned in each extremity, although weaker than normal. In eac patient, the symptoms of numbness, tingling, fatigue, and pain hav cleared and, in one, prolonged ulceration of a finger tip healed rapidl (Figures 66A and B). Full function of the arm remains and there h:

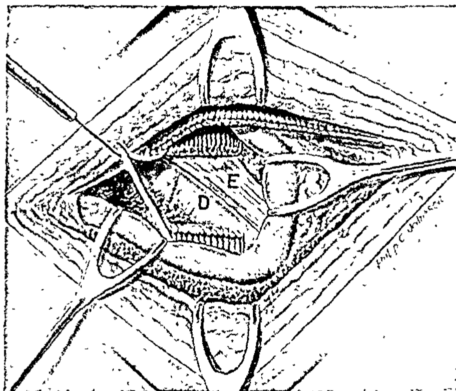


Figure 65 Exposure of subclavian artery (*D*) and brachial plexus (*E*).

been no deformity of the shoulder girdle (Figures 67 and 68). How wide the indication should be drawn for this operation must await further experience, especially after a longer period of follow-up of the early cases has been obtained.

Summary

1. The four causes of acute arterial occlusion have been discussed from the diagnostic and therapeutic points of view. It has been stressed

Figure 66A



Figure 66B

fifteen months. In those without thromboses, the radial pulse is strong in all positions of the arms and in those with thromboses, radial pulsation has returned in each extremity, although weaker than normal. In each patient, the *symptoms of numbness, tingling, fatigue, and pain* have cleared and, in one, prolonged ulceration of a finger tip healed rapidly (Figures 66A and B). Full function of the arm remains and there has

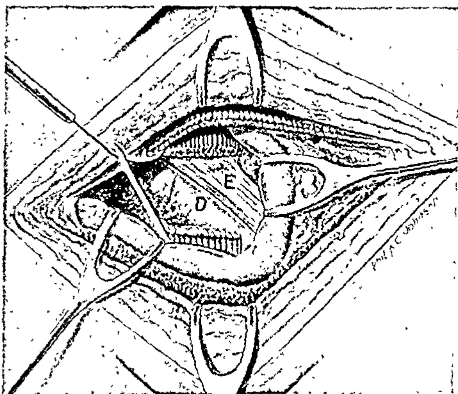


Figure 65 Exposure of subclavian artery (*D*) and brachial plexus (*E*).

been no deformity of the shoulder girdle (Figures 67 and 68). How wide the indication should be drawn for this operation must await further experience, especially after a longer period of follow-up of the early cases has been obtained

Summary

1. The four causes of acute arterial occlusion have been discussed from the diagnostic and therapeutic points of view. It has been stressed

in the majority of patients. Newer forms of surgical procedures are still on trial and have not as yet made a significant inroad on the widespread problem of peripheral arteriosclerotic occlusive vascular disease.

3. A new operative procedure has been described which has shown uniformly good early results in eight patients suffering from two or more of the shoulder-girdle syndromes of hyperabduction, scalenus anticus, costoclavicular, and cervical rib which had resulted in either temporary intermittent occlusion of the subclavian or axillary artery or in permanent thrombosis of the artery.



Figure 68

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Figure 67

that the clinical appraisal is sufficient for the application of proper therapeutic measures An attempt has been made to outline the indications for and contraindications to surgical intervention in each of these four categories of acute arterial occlusion.

2. The *role of surgical therapy in chronic arterial occlusion* has been critically evaluated and the need for the careful individualization of cases stressed. For the most part, a nonoperative regime is the one of choice

Chapter 19

CIRCULATORY RESPONSES TO LIFE SITUATIONS *

Stewart Wolf †

IT IS an old story that changes in cardiovascular function accompany emotional reactions such as anger or excitement. If this were the whole story there would be little point in reiterating it here. Only if such changes are actually pertinent to cardiovascular disorders and disease is it worth our while to dwell on them. Tonight I would like to summarize for you experimental evidence on that point gathered in collaboration with Drs. Harold Wolff, George Wolf, John Pfeiffer, Ian Stevenson, Charles Duncan, Robert Schneider, John Flynn, Herbert Ripley, and Phillipe Cardon. From the studies of these and other investigators it appears that certain cardiovascular changes set in motion by stressful life experiences may very well throw an important burden on the heart and the blood vessels.

Such studies have involved measurement of accessible indicators of cardiovascular function from among the various possibilities which may be grouped as follows

1. Mechanical design of heart pump—valves
2. Fuel for work—composition of coronary blood and caliber of vessels
3. Blood volume
4. Extent of peripheral vascular bed
5. Distensibility of peripheral vascular bed
6. Resistance of peripheral vascular bed

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† From the Department of Medicine, Cornell University Medical College-New York Hospital

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to yield any evidence of structural heart disease or other abnormality. It was noted that the occurrence of tachycardia at rest and two minutes after exercise was closely correlated with what went on in her daily life. Her conflicts were concerned mainly with her relationship with her rigid, demanding, diabetic mother.

At her first visit exercise tolerance (Figure 69) was considerably impaired. As the patient was followed in the clinic successive tests of ex-

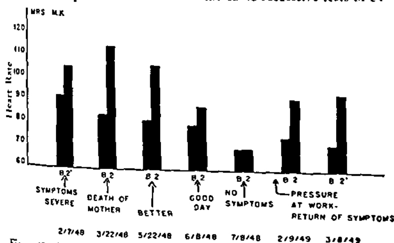


Figure 69. Repeated estimation of exercise tolerance under a variety of circumstances from day to day. The column above "B" represents the heart rate before exercise, above 2', the heart rate two minutes after the standard Master step test.

ercise tolerance were made. The second test was made a few days after the sudden death of the patient's mother to which she reacted with considerable guilt and depression. Although the resting heart rate was lower this day the exercise tolerance was impaired more than on the previous day. During the interviews which followed the patient was able to talk more freely about her relations with her parents and brother. She gained some understanding of her emotional development and in addition was reassured concerning the condition of her heart about which her symptoms had given added anxiety. In the three months following the death of her mother the patient gradually improved and became free of symptoms. Exercise tolerance was then normal.

The patient remained completely well for another seven months. At this time she arranged for her husband to obtain a job at her factory,

7. Blood viscosity
8. Stroke volume
9. Heart rate
10. Blood pressure

It has been shown that all of these functions that have been measured may become significantly altered during an individual's attempts to adapt to people and events in his environment.

Method. The various techniques and procedures involved in these studies are outlined in the original publications (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12). In general, the studies were carried out as follows:

Patients with various cardiovascular disturbances were collected and followed in a special clinic. They were studied with reference to background and life experience, attitudes and aspirations. These data were gathered from face-to-face interviews with the patient and other members of his family, from dreams, associations, slips of the tongue, gestures, and behavior. A diary record was kept from day to day in which events, attitudes, and reactions were correlated with the occurrence of symptoms and cardiovascular disturbances. When such observations indicated repeatedly a temporal coincidence between events provocative of significant personal conflict and measurable changes in cardiovascular function, one had presumptive evidence that the two might be related. The validity of this suspicion was then tested in a short-term experimental observation. Recordings were made during a control period of suitable length while the subject was relaxed and at ease. Then the topic of suspected conflict was introduced abruptly for discussion. When the reaction to this maneuver included the sought for cardiovascular change, the evidence was considered to have been strengthened After several minutes the "stress period" was terminated by strong reassurance on the part of the experimenter and attempts at diversion When the disturbance could thus be "turned off" it could be fairly concluded that the life situation and the cardiovascular response were indeed connected.

Results. In Figures 69–78 are illustrated sample results of the studies on various indicators of cardiovascular function

Heart rate and exercise tolerance. Figure 69 is a graph of repeated exercise tolerance tests performed on a 24-year-old housewife who complained of palpitation, chest pain, and dyspnea. Careful examination had failed

old her eldest sister died after a long illness. Shortly after this event the patient had her first attack of tachycardia, and continued to have about two attacks a year until the age of 19. When she was 19 the attacks ceased soon after she met the man she later married. A few years thereafter she was faced with the responsibilities of pregnancy, and she had a single attack during pregnancy. When the patient was 25 both her father and a sister to whom she was quite devoted died within a few weeks of each other She bore the immediate shock well, but a few weeks later began to be troubled by feelings of guilt toward her sister, whom she felt she had neglected Her sister appeared frequently in her dreams. While brooding thus she had two attacks within a week and continued to have others during the course of a reactive depression her mother suffered Attacks continued at about the same rate until, when the patient was 31, increasing tension and frustration in dealing with her domestic problems were associated with the increased frequency of attacks which brought her to the clinic.

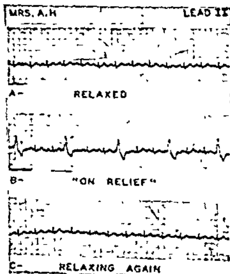


Figure 71 Abrupt occurrence of extrasystoles in a 55-year-old woman during a discussion of pertinent personal conflicts

Extrasystoles. The occurrence of extrasystoles during the contemplation of a stressful event is illustrated in Figure 71. The patient, a 55-year-old woman, complained of "nervousness"

The father of the patient was often depressed and her mother stern and domineering The patient gave early evidence of anxiety as a child in frequent nightmares, nail biting, and feelings of "nervousness" when in the company of her mother She had planned a career in music but at the age of 17, after the onset of bilateral chorioretinitis, abandoned it She was by no means incapacitated by her inadequate vision

intending to resign from her own job and have a baby. Her boss, who had obliged by giving her husband a job, hinted that he would discharge her husband if she left the company. *The patient felt frustrated and* tense, but was unable either to express her feelings to the boss or leave her job. In this setting she had a return of the former symptoms in milder degree. *Although her resting pulse rate was only slightly higher* than it had been, exercise tolerance was impaired and continued so for some months thereafter.

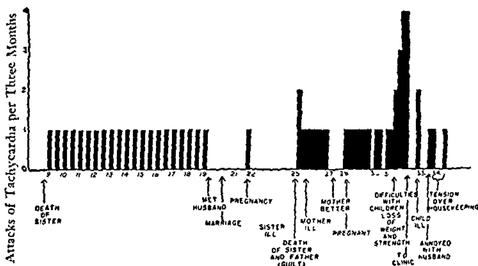


Figure 70 Diagrammatic representation of the frequency of attacks of paroxysmal tachycardia during the life of a 34-year-old housewife

Heart rhythm—paroxysmal tachycardia. Among the disturbances in rhythm which have been found to be correlated with the life situation is paroxysmal auricular tachycardia. The frequency of attacks over the period of the life of a 34-year-old housewife is illustrated in Figure 70.

The patient's father was a house painter of moderate means. Both her parents were "worriers" and both enforced a rather rigid discipline on the children who were required to participate in the family duties and responsibilities at an early age. Notwithstanding fear of her father and awe felt for her mother, the patient described her family as a "close" one in which the members were intimately dependent upon each other The patient said, "I think it was a happy childhood, but the sort in which one grew up before one's time " When the patient was 8 years

though she was presently complaining of excessive menstrual bleeding, there were no positive physical findings.

During the recording of the electrocardiogram the patient was interviewed Heart rate was initially normal although accelerated. She expressed profound worries about her health. As she expressed fear that her menorrhagia was due to cancer, she became agitated and began to weep Heart rate varied rapidly up to 140 and down to 128, then suddenly auricular fibrillation began.

Changes in electrocardiogram. During periods of significant conflict while discussing personal problems, a diminution in amplitude of the T wave of 0 5 mm or more was recorded in 18 subjects of 35 studied with and

Electrocardiographic changes in 35 patients	*No of patients showing change during period of emotional disturbance*
A. Increase in heart rate	
40 or more beats per minute	3
30 or more beats per minute	8
20 or more beats per minute	17
10 or more beats per minute	26
Less than 10 beats per minute	9
B Changes in rhythm	
All arrhythmias	9
Paroxysmal auricular fibrillation	1
Paroxysmal auricular tachycardia	1
Extrasystoles	8
Auricular	4
Nodal	2
Ventricular	6
C. Changes in electrocardiographic complexes	
Diminution in amplitude of T wave of more than 0 5 mm	18
Change in direction of T wave	8
ST depressions 0 5 mm or more	4
ST depressions less than 0 5 mm	2
P wave increased in amplitude	10
P wave decreased in amplitude	2

Figure 73 Summary of electrocardiographic changes observed during discussions of pertinent personal conflicts

and was able to get around easily and even to read large type. However, she did little for herself and subsided into a state of dependency upon her family, who, in turn, omitted her from the family councils and in general treated her like a child. After the death of her parents, a younger sister continued this practice, assumed supremacy among the siblings, handled all financial transactions, and freely directed the patient's life. In her thirties the patient became pregnant without marriage. Retrospectively at least, she felt that the man involved would have married her, but for the meddlesome interference of her family which drove him away. Her family urged her to allow the illegitimate child to be adopted, but she elected to raise him herself. This she did, not unsuccessfully, with the help of her family and some financial aid from the father. Relations with her sister continued to deteriorate and a few years before her first visit to the clinic palpitations began, associated with altercations with her sister. She finally withdrew from the latter's home and "went on relief." During an interview in the laboratory while connected with the electrocardiograph, frequent extrasystoles appeared as she answered the question, "How are you supporting yourself?"

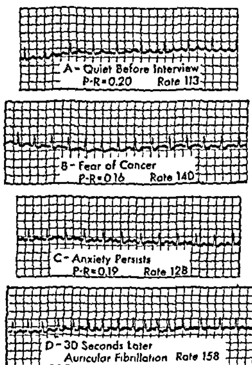


Figure 72. Abrupt occurrence of auricular fibrillation during discussion of pertinent personal conflicts.

Auricular fibrillation. Even such a major arrhythmia as auricular fibrillation was found to be related to stressful events in the life situation An example is illustrated in Figure 72. The patient was a 39-year-old housewife who had earlier undergone subtotal thyroidectomy for Graves' disease. At the present time basal metabolism rate was normal and, al-

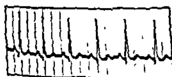
discussion of stressful topics. An example of such a finding is illustrated in Figure 76.

Renal blood flow. Another aspect of the circulation which has been thought to be closely connected with disease, especially in hypertension, is the renal blood flow. Accordingly, 35 subjects with essential hypertension and 13 normotensive subjects were studied by the techniques of Homer Smith (13). Effective renal plasma flow was estimated by clear-

Mr V C Lead II









A Quiet before exercise
B One minute after exercise
C. Six minutes after exercise
D. Two minutes later, anxious about heart

Figure 75. Similarity of electrocardiographic changes following exercise and during anxiety; note inversion of T wave in lead II

ance of para-aminohippurate and glomerular filtration by inulin-clearance.

The details of these studies have been reported elsewhere (2) but the prototype of the response is shown in Figure 77. Both hypertensive and control subjects whose blood pressure rose during the interview situation displayed evidence of renal vasoconstriction, with a sharp reduction in the effective renal plasma flow and an increased filtration fraction.

Comment Such changes as these would only be important if they were capable individually or collectively of making the patient sick. Since the heart has a great reserve capacity to meet short-term demands, it seems unlikely that any of these changes, when short-lived, has any important significance.

without heart disease. Other changes noted are summarized in Figure 73. An illustrative tracing is shown in Figure 74 in which a 49-year-old man was reminded of his anxiety about his heart. Such changes in the electrocardiographic complexes were very similar to those induced by

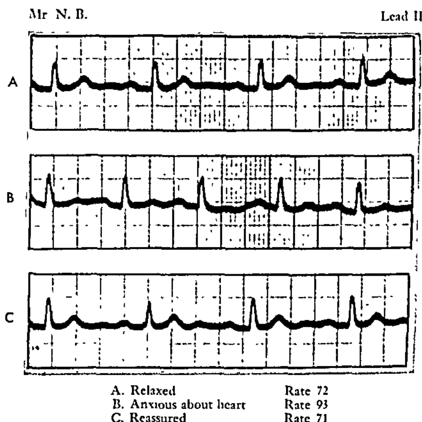


Figure 74. Depression of T wave in the electrocardiogram during a period of anxiety.

exercise in individuals with impaired coronary circulation as shown in Figure 75 (11)

Blood viscosity. In studies of changes in circulatory hemodynamics it has been customary for investigators to assume that blood viscosity will remain fairly constant for short periods in the absence of bleeding or serious trauma. In our own laboratory, however, Schneider (8), using the viscosimetric method of T'ang and Wang, found that blood viscosity increased as much as 20 per cent in company with pressor response to a

resistance and is required to fill a vascular bed of variable size. The adequacy of the heart in delivering blood to peripheral tissues depends directly on the quantity of blood pumped per unit time. The amount of work required to accomplish this job will vary not only with the demands of tissue metabolism but with the degree of peripheral resistance provided by arteriolar constriction or changes in blood viscosity. An

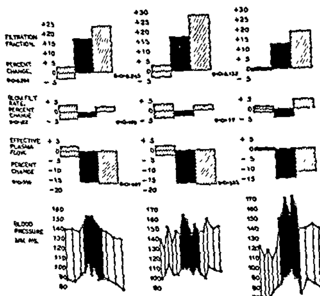


Figure 77 Changes in renal hemodynamics during pressor response to stress interview The blackened sections represent the stress period, and the cross-hatching the control periods before and after interview

increase in peripheral resistance will necessarily require more work of the heart and more oxygen consumption to maintain circulation

The balance of tissue demand and work done by the heart can be illuminated by recourse to the underlying physical principles which relate work done to maintain flow through a fluid system to pressure, viscosity, cross-sectional area, and length of the conduit (Figure 78)

It is evident that a decrease in peripheral resistance increases the flow of blood to peripheral tissues if blood pressure is maintained, just as removing the nozzle from a garden hose increases the flow of water As shown by the formula, if peripheral resistance is sharply reduced in

To presuppose cardiovascular damage it would probably be necessary to demonstrate sustained and significant increase in cardiac work or interference with the nutrition of the heart or vessels.

The adequacy of cardiac nutrition may be reflected by the electrocardiogram but it is not possible to draw very sweeping inferences from

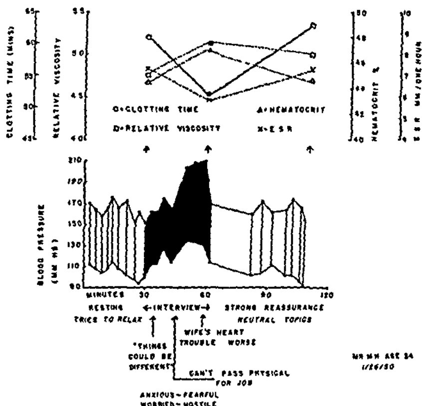


Figure 76. Increased blood viscosity and hematocrit associated with shortening of clotting time and sedimentation rate during a pressor response to a stress interview.

examination of heart waves. With the ballistocardiograph and other tools, however, it is possible to get a rough approximation of relative differences in cardiac work.

General hemodynamics. In ordinary stiff pipe pumping systems, the effectiveness of the circulation may be measured in terms of the efficiency of the pump and the actual work done. The effectiveness of the heart cannot be judged in these terms since it operates against a variable

an increase in peripheral resistance with stroke volume maintained the same

These facts probably explain why vigorous and prolonged exercise is so well tolerated by a healthy cardiovascular system It is well known that during exercise peripheral resistance is greatly reduced while stroke volume is increased. Our own experiments were performed with the ballistocardiograph immediately following 17 trips over the Master steps and at intervals of 5 and 10 minutes thereafter. While the ballistocardiograph may not be suitable for comparative determinations of cardiac output from individual to individual or even from day to day, it can reliably reflect relative differences in cardiac output in an individual subject when used more or less continuously in a single experiment.

Response to exercise and discussion of exercise. Measurements at rest and following exercise in 20 hypertensives and 28 healthy normotensive subjects are shown in Figure 80 Although the initial values in the two groups were different, the pattern of response was identical and included a sharp rise in stroke volume associated with a decreased peripheral resistance

It was unnecessary for the subject to actually take exercise in order to invoke the "exercise pattern" of cardiovascular adjustment Merely discussing the prospect of exercise with an individual who on previous occasions had undergone a double Master step procedure was sufficient to bring about the characteristic hemodynamic changes as shown in Figure 81

The hemodynamic pattern of high cardiac output and low peripheral resistance can be maintained over long periods of time without damage to the heart since in Graves' disease cardiac enlargement and ultimate failure are rare and late complications.

In essential hypertension, on the other hand, where it has been shown that peripheral resistance is increased and cardiac output and peripheral blood flow are on the low side of normal (15, 16), cardiac damage, enlargement, and failure are the rule.

It became desirable to ascertain under what circumstances these contrasting patterns of cardiovascular adaptation could be induced. As already pointed out, exercise was uniformly associated with increased output and lowering of peripheral resistance.

company with an increase in cardiac output a much bigger job of flooding the tissues with fresh blood can be accomplished with comparatively little increase in actual work being done by the heart. If, on the other hand, peripheral resistance is increased, blood pressure rises and more work is required by the heart to meet tissue needs since delivery per unit time to the tissue depends upon output per unit of time by the heart. Thus, within the limits encountered in a well-compensated circulation, it is convenient and fairly accurate to consider that increasing stroke

$$\text{WORK} = \frac{7\,QR}{6} + \frac{WV^2}{G}$$

Q = CARDIAC OUTPUT
R = RESISTANCE IN AORTA
W = WEIGHT OF BLOOD MOVED ($Q \times 1.05$)
V = MEAN SYSTOLIC VELOCITY

$$\left(\frac{\text{stroke volume}}{\text{cross section of aorta} \times 0.34\ \sqrt{\text{length of cardiac cycle}}}\right)$$

G = GRAVITY CONSTANT

Figure 78 Formula for expressing work of the heart "R," resistance in aorta, corresponds roughly to the mean blood pressure Changes in "R" reflect changes in peripheral resistance when "Q," cardiac output, remains constant

volume without an undue elevation of blood pressure is a relatively economical way to meet tissue demands while a rise in blood pressure without increased stroke volume is wasteful of energy and does not increase circulation

This inference receives added support from the work of Evans and Matsuoka (14) with heart-lung preparations in dogs Using the relationships contained in Poiseuille's law (Figure 79), they noted that cardiac

$$\text{BLOOD PRESSURE} = \frac{\text{length of artery} \times \text{viscosity} \times 8\ \pi \times \text{cardiac output}}{\text{cross-section area}^2}$$

Figure 79. Mathematical expression of Poiseuille's law Cross-section area reflects the contractile state of the arterioles

efficiency was greater when blood pressure was raised by an increase in stroke volume with peripheral resistance maintained the same than by

an increase in peripheral resistance with stroke volume maintained the same.

These facts probably explain why vigorous and prolonged exercise is so well tolerated by a healthy cardiovascular system It is well known that during exercise peripheral resistance is greatly reduced while stroke volume is increased. Our own experiments were performed with the ballistocardiograph immediately following 17 trips over the Master steps and at intervals of 5 and 10 minutes thereafter. While the ballistocardiograph may not be suitable for comparative determinations of cardiac output from individual to individual or even from day to day, it can reliably reflect relative differences in cardiac output in an individual subject when used more or less continuously in a single experiment.

Response to exercise and discussion of exercise. Measurements at rest and following exercise in 20 hypertensives and 28 healthy normotensive subjects are shown in Figure 80 Although the initial values in the two groups were different, the pattern of response was identical and included a sharp rise in stroke volume associated with a decreased peripheral resistance.

It was unnecessary for the subject to actually take exercise in order to invoke the "exercise pattern" of cardiovascular adjustment Merely discussing the prospect of exercise with an individual who on previous occasions had undergone a double Master step procedure was sufficient to bring about the characteristic hemodynamic changes as shown in Figure 81.

The hemodynamic pattern of high cardiac output and low peripheral resistance can be maintained over long periods of time without damage to the heart since in Graves' disease cardiac enlargement and ultimate failure are rare and late complications

In essential hypertension, on the other hand, where it has been shown that peripheral resistance is increased and cardiac output and peripheral blood flow are on the low side of normal (15, 16), cardiac damage, enlargement, and failure are the rule.

It became desirable to ascertain under what circumstances these contrasting patterns of cardiovascular adaptation could be induced. As already pointed out, exercise was uniformly associated with increased output and lowering of peripheral resistance.

Stressful interviews. Observations were made on the effect of stressful life experiences without exercise Data concerning the personality of each subject were derived from interviews with the patient and other members of his family, from associations, analysis of dream material, and psychological tests. A further appraisal of attitudes and motivations

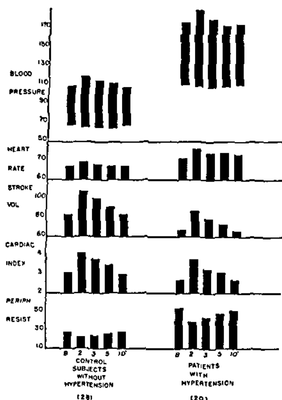


Figure 80. Hemodynamic changes before and after exercise as measured in normotensive and hypertensive subjects. "B" indicates before exercise, the numbers refer to determinations made 2, 3, 5, and 10 minutes after exercise.

of each subject was made by observation of his reactions especially during discussion of difficult life experiences, by things said and left unsaid, by gestures, slips of the tongue, blocking, projections and other indications in his behavior and stream of talk These data were then correlated with the symptoms and with the measurements of circulatory functions.

The first striking finding was that the type of cardiovascular disturbance encountered during relatively overt emotional disturbances—the kind any observer could recognize—was similar to that seen with

exercise, probably well tolerated by the body economy and of no significance in relation to disease (Figure 82). This may explain why obviously nervous patients with cardiac symptoms, so-called cardiac neurotics, live so long with healthy hearts. The cardiac overwork in increasing output is probably always short-lived because, unless exertion is undertaken, the peripheral blood supply will quickly exceed tissue demands, thus making the process a self-limiting one.

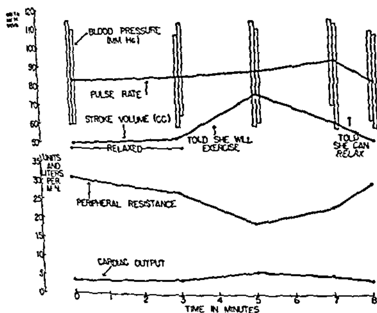


Figure 81 The "exercise pattern" of hemodynamic adaptation evoked in anticipation of exercise

The more costly pattern of cardiovascular adaptation was encountered when the patient subjected to significant emotional conflicts appeared calm and restrained and often altogether undisturbed (Figure 83). This pattern in which peripheral resistance is raised and cardiac output is not increased does not result in an increased supply of blood to tissues and can hence be maintained indefinitely without exceeding tissue demand so that this mechanism is self-perpetuating To put it another way, as long as peripheral resistance is high, the heart must continue to work harder than normal to maintain the same supply of

blood to the tissues. This pattern of reaction to stressful interviews was characteristically encountered in patients with essential hypertension.

It was not characteristic of all hypertensive patients, however. The possibility suggests itself that those patients who live for years with high blood pressure without cardiac or vascular damage may be those who have adopted the more economical hemodynamic pattern of high

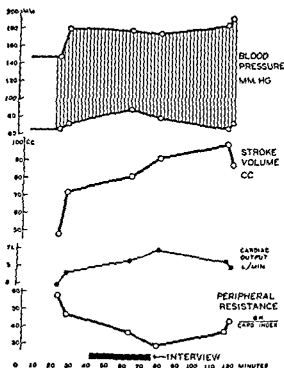


Figure 82. The "exercise pattern" of hemodynamic adaptation observed during a stressful interview

output and low resistance Since this pattern should be self-limiting in view of the fact that tissue needs are being exceeded by the increased peripheral circulation, it may not actually be present all the time. Whether or not this pattern when adopted actually is intermittent is not known. Since one cannot know the blood pressure except when one takes it, it is not possible to draw inferences about an individual's day to day arterial pressure Often the circumstances of attaching the sphygmomanometer cuff or merely being in the presence of the physician constitute an adequate stimulus to hypertension. For example, a 25-

year-old Armenian factory worker invariably had elevated blood pressure when the determination was made by his regular physician, a kindly but rather stern and quick-moving individual. Even after intravenous injections of Sodium Amytal with strong reassurance his arterial pressure remained high as shown in Figure 84. When, *on the other hand,*

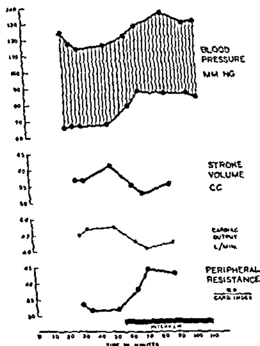


Figure 83 The "peripheral resistance pattern" of hemodynamic adaptation observed during a stressful interview.

another physician whom he considered more sympathetic took the blood pressure it was repeatedly and consistently much lower.

Even the so-called "standard" tests of blood pressure response are not valid indices of a prevailing hemodynamic state because the significance of the test often influences its effect on arterial pressure. For example, when one man, a 28-year-old steam fitter, thought that the decision as to whether or not he would undergo a mutilating sympathectomy hinged upon the outcome of a cold pressor test, he displayed the response of a "hyperreactor." Later the same day, when he was

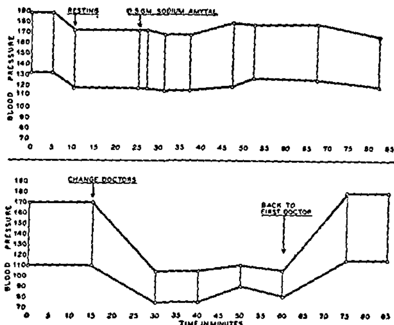


Figure 84. Effect of the prevailing situation on the level of blood pressure. Note the failure of intravenously administered Sodium Amytal to lower blood pressure in the presence of one physician On another day, blood pressure falls to normal level without drugs in the presence of a second physician

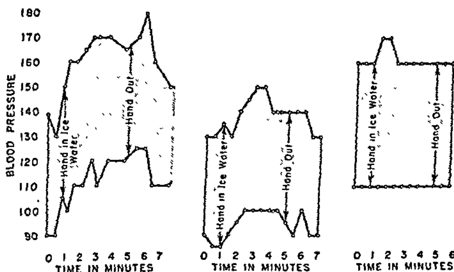


Figure 85. Variability of cold pressor response in the same individual. The first two tests were performed on the same day

reassured that the operation was not considered necessary, his blood pressure was lower initially and the test produced a "hyporeactive" response Even at times when his initial pressure was high, however, his response was "hyporeactive" when the performance of the test had no special significance for him (Figure 85).

Campbell and Blankenhorn (17) reported an interesting observation in 1925 which fits well this view of things. They found that certain hypertensives did not maintain their high blood pressure while they were asleep. These were the patients who had the least evidence of impairment of cardiovascular function. Schroeder and Goldman (18) also reported that the most benign cases of hypertension, those in whom Page (19) had earlier pointed out blotchy erythema and vascular lability, occurred in individuals who showed the most overt evidences of "nervousness" and "emotional lability"

On the other hand, the less evidently nervous, cautious, and restrained hypertensive appears to be the one with the poorer prognosis. From our studies he appears to be the one who utilizes more readily the pattern of increased peripheral resistance with a slight fall in cardiac output.

These possibilities are under investigation at the *present time*. The answers are not available as yet Suffice it, at present, to say that there are widespread cardiovascular adaptations to life stress, that these changes may be of the same nature and degree as those in response to other more concrete assaults from the environment, and that thus they may turn out to be highly pertinent to the pathogenesis of organic cardiovascular disease Certainly on the basis of the evidence at hand it behooves us as *clinicians* to accord serious attention to people and events, as well as other stresses in the lives of our cardiac patients.

What can be expected of this type of approach is, of course, not known. It hasn't been worked on very extensively and the results are hard to evaluate Nevertheless, an illustrative story of one of our hypertensive patients may be relevant

The patient was a 33-year-old Jewish dealer *in* illicit merchandise whose hypertension had developed in a setting of conflict with a domineering and punitive mother Against her will he had married an Irish Roman Catholic girl whose family equally disapproved of him For more than a year they each lived at their respective homes. The patient felt unable to commit himself to the responsibility of a menage of his

own. It was at this time that he was sent to us by his physician for consideration of sympathectomy because of sustained high levels of arterial pressure in the neighborhood of 170/120. Shortly after we began to follow him, his mother put him out of the home. He went to live with his in-laws under very crowded conditions. Here he became the object of repeated humiliations and verbal abuse, especially at the hands of one brother-in-law. During one of his visits at the hospital, he apparently got the impression that the author felt that it was unnecessary for him to continue quietly accepting this mistreatment. When he left the laboratory, where his blood pressure had been 155/110, he immediately looked up his brother-in-law and began to batter him with his fists After giving him a severe beating he phoned the hospital and said, "Doc, I better come right in. My pressure is probably high enough to break the machine." He did come and his blood pressure was recorded at normal for the first time, 125/85 (Figure 86). Ultimately, as we worked with this patient, it was possible for him to reorient his attitudes to the point where his self-confidence improved, he felt much less the need for restraint, and he got a job, moved into an apartment of his own with his wife. He was by no means well but the pattern of his reactions had changed a great deal His blood pressure was customarily within normal limits Where formerly anger and frustration had been associated with not only a rise in arterial pressure but also an uncontrollable desire to eat, he now found that he lost his appetite when he was upset, and discussion of topics which had formerly induced a brisk elevation of blood pressure no longer were capable of doing so (Figure 87)

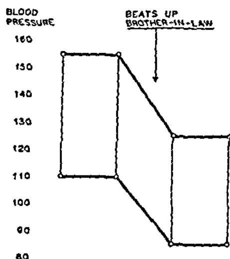


Figure 86 Abrupt fall in blood pressure following a relatively uninhibited expression of aggression.

So I repeat what I said earlier The data are not all in. The story is not complete but, from what we know at present, it is clear that the

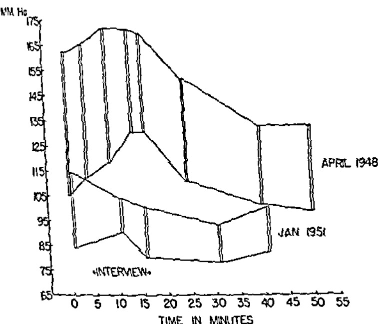


Figure 87 Change in reactivity in an individual after a three-year period. Initially, he was hypertensive and reacted to a discussion of personal problems with a brisk elevation of blood pressure. Later when he had lost evidence of hypertension and when his attitude had changed in a number of other ways, he no longer displayed a pressor response but actually showed a drop of blood pressure during a discussion of stressful topics

intelligent management of hypertension among other cardiovascular disorders includes attention to the patient as a person and his reactions to the stresses of day to day life.

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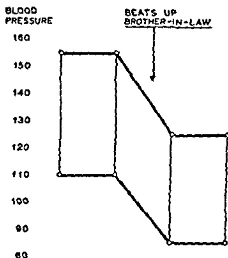


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